TITLE OF THE INVENTION

TYROSINE KINASE INHIBITORS

BACKGROUND OF THE INVENTION

Protein kinases (PKs) are enzymes that catalyze the phosphorylation of hydroxy groups on tyrosine, serine and threonine residues of proteins. The consequences of this seemingly simple activity are staggering; cell growth, differen-tiation and proliferation; i.e., virtually all aspects of cell life, in one way or another depend on PK activity. Furthermore, abnormal PK activity has been related to a host of disorders, ranging from relatively non life-threatening diseases such as psoriasis to extremely virulent diseases such as glioblastoma (brain cancer). PKs can be broken into two classes, the protein tyrosine kinases (PTKs) and the serine-threonine kinases (STKs).

Certain growth factor receptors exhibiting PK activity are known as receptor tyrosine kinases (RTKs). They comprise a large family of transmembrane receptors with diverse biological activity. As present, at least nineteen (19) distinct subfamilies of RTKs have been identified. One RTK subfamily contains the insulin receptor (IR), insulin-like growth factor I receptor (IGF-1R) and insulin receptor related receptor (IRR). IR and IGF-1R interact with insulin to activate a hetero-tetramer composed of two entirely extracellular glycosylated α subunits and two β subunits which cross the cell membrane and which contain the tyrosine kinase domain. The Insulin-like Growth Factor-1 Receptor (IGF-1R), and its ligands, IGF-1 and IGF-2, are abnormally expressed in numerous tumors, including, but not limited to, breast, prostate, thyroid, lung, hepatoma, colon, brain, neuroendocrine, and others.

A more complete listing of the known RTK subfamilies is described in Plowman et al., KN&P, 1994, 7(6):334-339 which is incorporated by reference, including any drawings, as if fully set forth herein.

In addition to the RTKs, there also exists a family of entirely intracellular PTKs called "non-receptor tyrosine kinases" or "cellular tyrosine kinases." This latter designation, abbreviated "CTK", will be used herein. CTKs do not contain extracellular and transmembrane domains. At present, over 24 CTKs in 11 subfamilies (Src, Frk, Btk, Csk, Abl, Zap70, Fes, Fps, Fak, Jak and Ack) have been identified. The Src subfamily appears so far to be the largest group of CTKs and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk. For a more detailed discussion of CTKs, see Bolen, Oncogene, 1993, 8:2025-2031, which is incorporated by reference, including any drawings, as if fully set forth herein.

RTKs, CTKs and STKs have all been implicated in a host of pathogenic conditions including significantly, cancer. Other pathogenic conditions, which have been

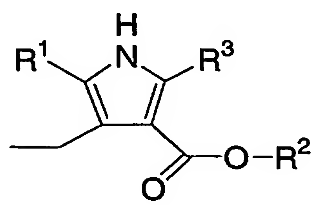
associated with PTKs include, without limitation, psoriasis, hepatic cirrhosis, diabetes, atherosclerosis, angiogenesis, restenosis, ocular diseases, rheumatoid arthritis and other inflammatory disorders, autoimmune diseases and a variety of renal disorders.

SUMMARY OF THE INVENTION

The present invention relates to compounds that are capable of inhibiting, modulating and/or regulating signal transduction of both receptor-type and non-receptor type tyrosine kinases. The compounds of the instant invention possess a core structure that comprises a substituted pyrrole moiety. The present invention is also related to the pharmaceutically acceptable salts and stereoisomers of these compounds.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of kinases and are illustrated by a compound of Formula I:



I

wherein

R^1 is selected from

1) hydrogen,
2) halogen,
3) substituted or unsubstituted C_1-C_{10} alkyl,
4) substituted or unsubstituted C_2-C_{10} alkenyl,
5) substituted or unsubstituted C_2-C_{10} alkynyl,
6) substituted or unsubsituted aryl,
7) substituted or unsubstituted C_3-C_{10} cycloalkyl,
8) substituted or unsubstituted heterocyclyl,
9) $-(CR^a{}_2)_nOR^4$, and
10) $-(CR^a{}_2)_tC(O)OR^4$;

said alkyl, alkenyl, alkynyl, aryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more of R^7;

R^2 is selected from

1) hydrogen,
2) substituted or unsubstituted aralkyl,
3) substituted or unsubstituted C_1-C_{10} alkyl,
4) substituted or unsubstituted heterocyclyl,
5) substituted or unsubstituted aryl, and
6) substituted or unsubstituted C_3-C_{10} cycloalkyl;

R^3 is selected from

1) hydrogen,
2) halogen,
3) $-C(O)R^4$,
4) substituted or unsubstituted C_1-C_{10} alkyl,
5) substituted or unsubstituted aryl,
6) substituted or unsubstituted heterocyclyl,
7) substituted or unsubstituted C_3-C_{10} cycloalkyl,
8) substituted or unsubstituted C_2-C_{10} alkenyl, and
9) substituted or unsubstituted C_2-C_{10} alkynyl;

R^4 is independently selected from

1) hydrogen,
2) substituted or unsubstituted C_1-C_{10} alkyl,
3) substituted or unsubstituted aryl,
4) substituted or unsubstituted heterocyclyl,
5) substituted or unsubstituted C_3-C_{10} cycloalkyl,
6) substituted or unsubstituted C_2-C_{10} alkenyl, and
7) substituted or unsubstituted C_2-C_{10} alkynyl;

R^6 is independently selected from

1) substituted or unsubstituted aryl,
2) substituted or unsubstituted heterocyclyl,
3) substituted or unsubstituted cycloalkyl, and

4) halogen;

R^7 is independently selected from

1) hydrogen,
2) halogen,
3) substituted or unsubstituted C_1-C_{10} alkyl,
4) substituted or unsubstituted C_2-C_{10} alkenyl,
5) substituted or unsubstituted C_2-C_{10} alkynyl,
6) substituted or unsubstituted C_3-C_{10} cycloalkyl,
7) substituted or unsubstituted aryl,
8) substituted or unsubstituted heterocyclyl,
9) $-NO_2$,
10) $-NR_4(CR^a{}_2)_nC(O)R^4$,
11) $-(CR^a{}_2)_nNR^4{}_2$,
12) $-(CR^a{}_2)_nNR^4(CR^a{}_2)_nR^6$,
13) $-CN$,
14) $-(CR^a{}_2)_nC(O)R^4$,
15) $-(CR^a{}_2)_nC(O)(CR^a{}_2)_nOR^4$,
16) $-(CR^a{}_2)_nOR^4$,
17) $-(CR^a{}_2)_nR^6$,
18) $-(CR^a{}_2)_nC(O)OR^4$, and
19) $-(CR^a{}_2)_nSi(R^4)_3$;

R^a is independently selected from

1) hydrogen,
2) substituted or unsubstituted C_1-C_{10} alkyl,
3) substituted or unsubstituted C_2-C_{10} alkenyl,
4) substituted or unsubstitute C_2-C_{10} alkynyl,
5) $-OR^4$,
6) $-C(O)OR^4$,
7) $-NR^4{}_2$,
8) substituted or unsubstituted aryl,
9) substituted or unsubstituted heterocyclyl, and
10) substituted or unsubstituted C_3-C_{10} cycloalkyl;

n is independently 0 to 6;

t is 1 to 4;

or a pharmaceutically acceptable salt or stereoisomer thereof.

A second embodiment of the instant invention is a compound of Formula I, or a pharmaceutically acceptable salt or stereoisomer thereof, as described above, wherein

R^1 is selected from

1) hydrogen,
2) halogen,
3) substituted or unsubstituted C_1-C_6 alkyl,
4) substituted or unsubstituted C_2-C_{10} alkynyl,
5) substituted or unsubsituted aryl,
6) substituted or unsubstituted C_3-C_{10} cycloalkyl, and
7) substituted or unsubstituted heterocyclyl;

said alkyl, alkynyl, aryl, cycloalkyl, and heterocyclyl is optionally substituted with one or more of R^7;

R^2 is selected from

1) substituted or unsubstituted aralkyl,
2) substituted or unsubstituted C_1-C_6 alkyl,
3) substituted or unsubstituted aryl, and
4) substituted or unsubstituted C_3-C_{10} cycloalkyl;

R^3 is selected from

1) halogen,
2) $-C(O)R^4$, and
3) substituted or unsubstituted C_1-C_6 alkyl;

R^4 is independently selected from

1) hydrogen,
2) substituted or unsubstituted C_1-C_6 alkyl,
3) substituted or unsubstituted aryl,

4) substituted or unsubstituted heterocyclyl, and
5) substituted or unsubstituted C_3-C_{10} cycloalkyl;

and all other substituents and variables are as defined above.

A third embodiment of the instant invention is a compound of Formula I, or a pharmaceutically acceptable salt or stereoisomer thereof, as described above, wherein

R^1 is selected from
1) substituted or unsubstituted C_1-C_6 alkyl,
2) substituted or unsubstituted C_2-C_{10} alkynyl,
3) substituted or unsubstituted heterocyclyl and
4) substituted or unsubstituted aryl;

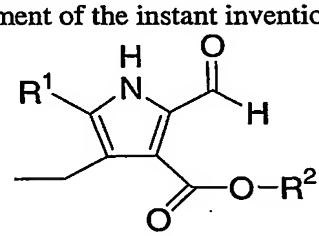
said alkyl, alkynyl, heterocyclyl and aryl is optionally substituted with one or more of R^7;

R^2 is selected from
1) substituted or unsubstituted aralkyl, and
2) substituted or unsubstituted C_1-C_6 alkyl;

R^3 is selected from
1) halogen, and
2) $-C(O)R^4$;

and all other substituents and variables are as defined above.

A fourth embodiment of the instant invention is a compound of Formula II:



II

wherein

R^1 is selected from

1) hydrogen,
2) halogen,
3) substituted or unsubstituted C_1-C_6 alkyl,
4) substituted or unsubstituted C_2-C_{10} alkynyl,
5) substituted or unsubstituted aryl,
6) substituted or unsubstituted C_3-C_{10} cycloalkyl, and
7) substituted or unsubstituted heterocyclyl;

said alkyl, alkynyl, aryl, cycloalkyl and heterocyclyl is optionally substituted with one or more of R^7;

R^2 is selected from

1) substituted or unsubstituted aralkyl, and
2) substituted or unsubstituted C_1-C_6 alkyl;

R^4 is independently selected from

1) hydrogen,
2) substituted or unsubstituted C_1-C_{10} alkyl,
3) substituted or unsubstituted aryl,
4) substituted or unsubstituted heterocyclyl,
5) substituted or unsubstituted C_3-C_{10} cycloalkyl,
6) substituted or unsubstituted C_2-C_{10} alkenyl, and
7) substituted or unsubstituted C_2-C_{10} alkynyl;

R^6 is independently selected from

1) substituted or unsubsituted aryl,
2) substituted or unsubstituted heterocyclyl,
3) substituted or unsubstituted C_3-C_{10} cycloalkyl, and
4) halogen;

R^7 is independently selected from

1) hydrogen,
2) halogen,
3) substituted or unsubstituted C_1-C_{10} alkyl,
4) substituted or unsubstituted C_2-C_{10} alkenyl,
5) substituted or unsubstituted C_2-C_{10} alkynyl,

6) substituted or unsubstituted C_3-C_{10} cycloalkyl,
7) substituted or unsubstituted aryl,
8) substituted or unsubstituted heterocyclyl,
9) $-NO_2$,
10) $-NR^4(CR^a_2)_nC(O)R^4$,
11) $-(CR^a_2)_nNR^4_2$,
12) $-(CR^a_2)_nNR^4(CR^a_2)_nR^6$,
13) $-CN$,
14) $-(CR^a_2)_nC(O)R^4$,
15) $-(CR^a_2)_nC(O)(CR^a_2)_nOR^4$,
16) $-(CR^a_2)_nOR^4$,
17) $-(CR^a_2)_nR^6$,
18) $-(CR^a_2)_nC(O)OR^4$, and
19) $-(CR^a_2)_nSi(R^4)_3$;

R^a is independently selected from
1) hydrogen,
2) substituted or unsubstituted C_1-C_{10} alkyl,
3) substituted or unsubstituted C_1-C_{10} alkenyl,
4) substituted or unsubstitute C_1-C_{10} alkynyl,
5) $-OR^4$,
6) $-C(O)OR^4$,
7) $-NR^4_2$,
8) substituted or unsubstituted aryl,
9) substituted or unsubstituted heterocyclyl, and
10) substituted or unsubstituted C_3-C_{10} cycloalkyl;

n is independently 0 to 6;
t is 1 to 4;

or a pharmaceutically acceptable salt or stereisomer thereof.

Examples of compounds of the instant invention include

benzyl 4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2,5-diiodo-1H-pyrrole-3-carboxylate;

methyl 5-(4-fluorophenyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-thien-2-yl-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-[3-(trimethylsilyl)prop-1-ynyl]-1H-pyrrole-3-carboxylate;

4'-benzyl 1-tert-butyl 3'-ethyl-5'-formyl-1H,1'H-2,2'-bipyrrole-1,4'-dicarboxylate;

benzyl 5-(3,5-dimethylisoxazol-4-yl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

benzyl 5-(1-benzofuran-2-yl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

benzyl 4-ethyl-2-formyl-5-(3-nitrophenyl)-1H-pyrrole-3-carboxylate;

benzyl 4-ethyl-2-formyl-5-(5-methyl-2-furyl)-1H-pyrrole-3-carboxylate;

benzyl 5-[3-(acetylamino)phenyl]-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

benzyl 4-ethyl-2-formyl-5-pyridin-4-yl-1H-pyrrole-3-carboxylate;

benzyl 4-ethyl-2-formyl-5-phenyl-1H-pyrrole-3-carboxylate;

benzyl 5-(3-cyanophenyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

benzyl 4-ethyl-2-formyl-5-(3-methoxyphenyl)-1H-pyrrole-3-carboxylate;

benzyl 4-ethyl-2-formyl-5-(5-formyl-2-furyl)-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-(phenylethynyl)-1H-pyrrole-3-carboxylate;

methyl 5-{3-[benzyl(methyl)amino]prop-1-ynyl}-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

benzyl 5-(2-cyanophenyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

benzyl 5-(4-cyanophenyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

benzyl 4-ethyl-2-formyl-5-(4-nitrophenyl)-1H-pyrrole-3-carboxylate;

benzyl 4-ethyl-2-formyl-5-(2-methoxyphenyl)-1H-pyrrole-3-carboxylate;

benzyl 4-ethyl-2-formyl-5-(4-methoxyphenyl)-1H-pyrrole-3-carboxylate;

benzyl 4-ethyl-2-formyl-5-(2-methylphenyl)-1H-pyrrole-3-carboxylate;

benzyl 4-ethyl-2-formyl-5-(3-methylphenyl)-1H-pyrrole-3-carboxylate;

benzyl 5-(2-chlorophenyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

benzyl 5-(3-chlorophenyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-[1-(3-hydroxypropyl)vinyl]-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-(5-hydroxypent-1-ynyl)-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-[(1-hydroxycyclohexyl)ethynyl]-1H-pyrrole-3-carboxylate;

methyl 5-[3-(dimethylamino)prop-1-ynyl]-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

methyl 5-(3,3-dimethylbut-1-ynyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-(pyridin-2-ylethynyl)-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-(6-methoxypyridin-2-yl)-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-(3-methoxyprop-1-ynyl)-1H-pyrrole-3-carboxylate;

methyl 5-[(2-bromophenyl)ethynyl]-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

methyl 5-[3-(1H-1,2,3-benzotriazol-1-yl)prop-1-ynyl]-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-5-(2-ethylbutyl)-2-formyl-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-(4-methylpyridin-2-yl)-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-(6-methylpyridin-2-yl)-1H-pyrrole-3-carboxylate;

methyl 5-(4-tert-butylphenyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

methyl 5-(2,4-difluorophenyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-[3-(methoxycarbonyl)phenyl]-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-[4-(methoxycarbonyl)phenyl]-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-[(1-hydroxycyclopentyl)ethynyl]-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-(3-hydroxy-3-methylbut-1-ynyl)-1H-pyrrole-3-carboxylate

methyl 4-ethyl-2-formyl-5-(1-hexylvinyl)-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-(1,3-thiazol-2-yl)-1H-pyrrole-3-carboxylate;

methyl 5-[1-(3-chloropropyl)vinyl]-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

methyl 5-(5-chloropent-1-ynyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-(3-hydroxy-3-phenylbut-1-ynyl)-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-(3-methylpyridin-2-yl)-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-isopentyl-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-(3-methylthien-2-yl)-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-isobutyl-1H-pyrrole-3-carboxylate;

methyl 5-cyclohexyl-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

methyl 5-butyl-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

methyl 5-cyclopentyl-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

methyl 5-(cyclohexylmethyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

methyl 5-sec-butyl-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-(3-methoxy-2-methyl-3-oxopropyl)-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-phenyl-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-pyridin-4-yl-1H-pyrrole-3-carboxylate;

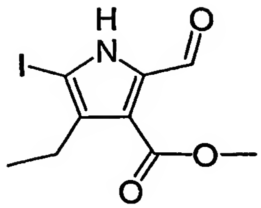
methyl 4-ethyl-2-formyl-5-(4-nitrophenyl)-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-(2-methoxyphenyl)-1H-pyrrole-3-carboxylate;

or the pharmaceutically acceptable salts or stereoisomers thereof.

Specific examples of compounds of the instant invention include

methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate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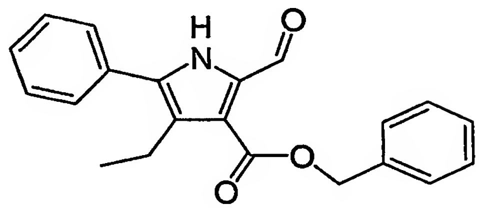
benzyl 4-ethyl-2-formyl-5-phenyl-1H-pyrrole-3-carboxylate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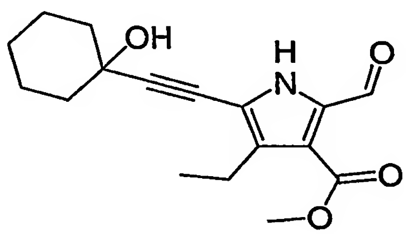
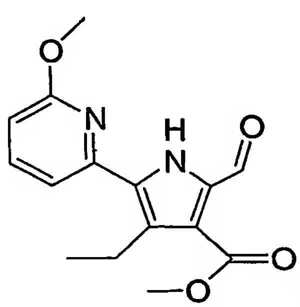
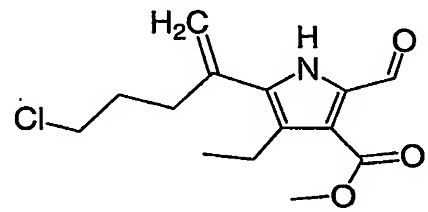
methyl 4-ethyl-2-formyl-5-[(1-hydroxycyclohexyl)ethynyl]-1H-pyrrole-3-carboxylate


;

methyl 4-ethyl-2-formyl-5-(6-methoxypyridin-2-yl)-1H-pyrrole-3-carboxylate


;

methyl 5-[1-(3-chloropropyl)vinyl]-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



;

or a pharmaceutically acceptable salt or stereoisomer thereof.

A further embodiment of the instant invention is a trifluroacetic acid salt of the compound

methyl 4-ethyl-2-formyl-5-(6-methoxypyridin-2-yl)-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-(4-methylpyridin-2-yl)-1H-pyrrole-3-carboxylate;

methyl 4-ethyl-2-formyl-5-(6-methylpyridin-2-yl)-1H-pyrrole-3-carboxylate;
benzyl 4-ethyl-2-formyl-5-pyridin-4-yl-1H-pyrrole-3-carboxylate.

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, being included in the present invention. In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted or named.

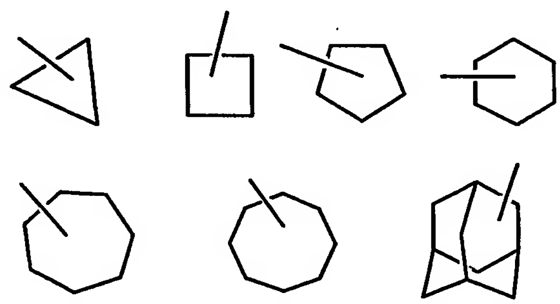
When any variable (e.g. aryl, heterocycle, R^4, R^a etc.) occurs more than one time in any substituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques

known in the art, as well as those methods set forth below, from readily available starting materials.

As used herein, "alkyl" is intended to include both branched and straight-chain aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, C_1-C_{10}, as in "C_1-C_{10} alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear or branched arrangement. For example, "C_1-C_{10} alkyl" specifically includes methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and so on.

"Cycloalkyl" as used herein is intended to include non-aromatic cyclic hydrocarbon groups, having the specified number of carbon atoms, which may or may not be bridged or structurally constrained. Examples of such cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, cyclooctyl, cycloheptyl, tetrahydro-naphthalene, methylenecylohexyl, and the like. As used herein, examples of "C_3 – C_{10} cycloalkyl" may include, but are not limited to:



If no number of carbon atoms is specified, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to 4 non-aromatic carbon-carbon double bonds may be present. Thus, "C_2-C_6 alkenyl" means an alkenyl radical having from 2 to 6 carbon atoms. Alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Up to 3 carbon-carbon triple bonds may be present. Thus, "C_2-C_6 alkynyl" means an alkynyl radical having from 2 to 6 carbon atoms. Alkynyl groups include ethynyl, propynyl and

butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, indanyl, indanonyl, indenyl, biphenyl, tetralinyl, tetralonyl, fluorenonyl, phenanthryl, anthryl, acenaphthyl, tetrahydronaphthyl, and the like.

As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro, fluoro, bromo and iodo.

The term heteroaryl, as used herein, represents a stable monocyclic or bicyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzimidazolyl, benzodioxolyl, benzotriazolyl, benzothiofuranyl, benzothiazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, benzoquinolinyl, imidazolyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrahydronaphthyl, tetrahydroquinoline, and the like.

The term heterocycle or heterocyclic or heterocyclyl, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. "Heterocycle" or "heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrathydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited to the following: azepanyl, azetidinyl, benzimidazolyl, benzodioxolyl, benzofuranyl, benzofurazanyl, benzopyranyl, benzopyrazolyl, benzotriazolyl, benzothiazolyl, benzothienyl, benzothiofuranyl, benzothiophenyl, benzothiopyranyl, benzoxazepinyl, benzoxazolyl, carbazolyl, carbolinyl, chromanyl, cinnolinyl, diazepanyl, diazapinonyl, dihydrobenzofuranyl, dihydrobenzofuryl, dihydrobenzoimidazolyl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrocyclopentapyridinyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisoquinolinyl, dihydroisothiazolyl, dihydrooxadiazolyl,

dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, dioxanyl, dioxidotetrahydrothienyl, dioxidothiomorpholinyl, furyl, furanyl, imidazolyl, imidazolinyl, imidazolidinyl, imidazothiazolyl, imidazopyridinyl, indazolyl, indolazinyl, indolinyl, indolyl, isobenzofuranyl, isochromanyl, isoindolyl, isoindolinyl, isoquinolinone, isoquinolyl, isothiazolyl, isothiazolidinyl, isoxazolinyl, isoxazolyl, methylenedioxybenzoyl, morpholinyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazolinyl, oxetanyl, oxoazepinyl, oxadiazolyl, oxidothiomorpholinyl, oxodihydrophthalazinyl, oxodihydroindolyl, oxoimidazolidinyl, oxopiperazinyl, oxopiperdinyl, oxopyrrolidinyl, oxopyrimidinyl, oxopyrrolyl, oxotriazolyl, piperidyl, piperidinyl, piperazinyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinonyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, pyrrolidinyl, quinazolinyl, quinolinyl, quinolyl, quinolinonyl, quinoxalinyl, tetrahydrocycloheptapyridinyl, tetrahydrofuranyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydropyranyl, tetrahydroquinolinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thiazolinyl, thienofuryl, thienyl, thiomorpholinyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, and the like. In an embodiment of the invention, heterocycle is selected from oxoazepinyl, benzimidazolyl, diazepanyl, diazapinonyl, imidazolyl, oxoimidazolidinyl, indolyl, isoquinolinyl, morpholinyl, piperidyl, piperazinyl, pyridyl, pyrrolidinyl, oxopiperidinyl, oxopyrimidinyl, oxopyrrolidinyl, quinolinyl, tetrahydrofuryl, tetrahydrofuranyl, tetrahydroisoquinolinyl, thienyl, furyl, furanyl, pyrazinyl, benzofuranyl, isoxazolyl, pyrrolyl, thiazolyl, benzothienyl, dihydroisoquinolinyl, azepanyl, thiomorpholinyl, dioxanyl, dioxidotetrahydrothienyl, imidazothiazolyl, benzothiazolyl, and triazolyl. In another embodiment of the invention, heterocycle is selected from benzofuranyl, thienyl, pyrrolyl, isoxazolyl, furyl, pyridyl, benzotriazolyl, and thiazolyl.

As used herein, "aralkyl" is intended to mean an aryl moiety, as defined above, attached through a C_1-C_{10} alkyl linker, where alkyl is defined above. Examples of aralkyls include, but are not limited to, benzyl, naphthylmethyl and phenylpropyl. In an embodiment of this invention, aralkyl is benzyl.

As used herein, "heterocyclylalkyl" is intended to mean a heterocyclic moiety, as defined below, attached through a C_1-C_{10} alkyl linker, where alkyl is defined above. Examples of heterocyclylalkyls include, but are not limited to, pyridylmethyl, imidazolylethyl, pyrrolidinylmethyl, morpholinylethyl, quinolinylmethyl, imidazolylpropyl and the like.

As used herein, the terms "substituted C_1-C_{10} alkyl", "substituted C_2-C_{10} alkenyl", and "substituted C_2-C_{10} alkynyl" are intended to include the branch or straight-chain alkyl group of the specified number of carbon atoms, wherein the carbon atoms may be substituted with 1 to 3 substituents selected from the group which includes, but is not limited to, halo, C_1-C_{20} alkyl, CF_3, NH_2, $N(C_1$-C_6 alkyl$)_2$, NO_2, oxo, CN, N_3, -OH, -O(C_1-C_6 alkyl), C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_0-C_6 alkyl) $S(O)_{0-2}$-, (C_0-C_6 alkyl)$S(O)_{0-2}$(C_0-C_6 alkyl), (C_0-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, -O(C_1-C_6 alkyl)CF_3, (C_0-C_6 alkyl)C(O)-, (C_0-C_6 alkyl)OC(O)-, (C_0-C_6 alkyl) O(C_1-C_6 alkyl)-, (C_0-C_6 alkyl)$C(O)_{1-2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl)OC(O)NH-, aryl, aralkyl, heterocycle, heterocyclylalkyl, halo-aryl, halo-aralkyl, halo-heterocycle, halo-heterocyclylalkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano-heterocyclylalkyl.

As used herein, the terms "substituted C_3-C_{10} cycloalkyl", "substituted aryl", and "substituted heterocycle", are intended to include the cyclic group containing from 1 to 3 substituents in addition to the point of attachment to the rest of the compound. Preferably, the substituents are selected from the group which includes, but is not limited to, halo, C_1-C_{20} alkyl, CF_3, NH_2, $N(C_1$-C_6 alkyl$)_2$, NO_2, oxo, CN, N_3, -OH, -O(C_1-C_6 alkyl), C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_0-C_6 alkyl) $S(O)_{0-2}$-, (C_0-C_6 alkyl)$S(O)_{0-2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, -O(C_1-C_6 alkyl)CF_3, (C_0-C_6 alkyl)C(O)-, (C_0-C_6 alkyl)OC(O)-, (C_0-C_6alkyl)O(C_1-C_6 alkyl)-, (C_0-C_6 alkyl)$C(O)_{1-2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl)OC(O)NH-, aryl, aralkyl, heteroaryl, heterocyclylalkyl, halo-aryl, halo-aralkyl, halo-heterocycle, halo-heterocyclylalkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano-heterocyclylalkyl.

As used herein, the phrase "substituted with at least one substituent" is intended to mean that the substituted group being referenced has from 1 to 6 substituents. Preferably, the substituted group being referenced contains from 1 to 3 substituents, in addition to the point of attachment to the rest of the compound.

In an embodiment of this invention, R^1 is hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_{10} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted C_3-C_{10} cycloalkyl, or substituted or unsubstituted heterocyclyl.

In another embodiment of this invention, R^1 is substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_{10} alkynyl, substituted or unsubstituted aryl, or substituted or unsubstituted heterocyclyl.

In a further embodiment of this invention, R^1 is substituted or unsubstiuted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_{10} alkynyl, substituted or unsubstituted phenyl, or substituted or unsubstituted heterocycle selected from benzofuranyl, thienyl, pyrrolyl, isoxazolyl, furyl, pyridyl, benzotriazolyl, and thiazolyl.

In an embodiment of this invention, R^2 substituted or unsubstituted aralkyl, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted aryl or substituted or unsubstituted C_3-C_{10} cycloalkyl.

In another embodiment of this invention, R^2 is substituted or unsubstituted aralkyl or substituted or unsubstituted C_1-C_6 alkyl.

In a further embodiment of this invention, R^2 is substituted or unsubstituted benzyl or substituted or unsubstituted C_1-C_6 alkyl.

In an embodiment of this invention, R^3 is hydrogen, halogen, -C(O)R4 or substituted or unsubstituted C_1-C_6 alkyl. In a further embodiment of this invention, R^3 is –C(O)R^4.

In an embodiment of this invention, n is independently 0, 1, 2, 3 or 4. In another embodiment of this invention, n is independently 0, 1, 2 or 3.

In an embodiment of this invention, t is independently 1, 2, 3 or 4. In a further embodiment of this invention, t is independently 3.

It is intended that the definition of any substituent or variable (e.g., R^4, R^a, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, -$N(R^4)_2$ represents -NHH, -$NHCH_3$, -NHC_2H_5, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

For use in medicine, the salts of the compounds of Formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared form pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium,

calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine caffeine, choline, N, N^1-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric and tartaric acids.

The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977:66:1-19.

It will also be noted that the compounds of the present invention are potentially internal salts or zwitterions, since under physiological conditions a deprotonated acidic moiety in the compound, such as a carboxyl group, may be anionic, and this electronic charge might then be balanced off internally against the cationic charge of a protonated or alkylated basic moiety, such as a quaternary nitrogen atom.

Abbreviations, which may be used in the description of the chemistry and in the Examples that follow, include:

Ac_2O	Acetic anhydride;
AcOH	Acetic acid;
AIBN	2,2'-Azobisisobutyronitrile;
Ar	Aryl;
BINAP	2,2'-Bis(diphenylphosphino)-1,1' binaphthyl;
Bn	Benzyl;
BOC/Boc	*tert*-Butoxycarbonyl;
BSA	Bovine Serum Albumin;

CAN	Ceric Ammonia Nitrate;
CBz	Carbobenzyloxy;
CI	Chemical Ionization;
DBAD	Di-*tert*-butyl azodicarboxylate;
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene;
DCC	1,3-Dichlorohexylcarbodiimide;
DCE	1,2-Dichloroethane;
DCM	Dichloromethane;
DIEA	*N,N*-Diisopropylethylamine;
DMAP	4-Dimethylaminopyridine;
DME	1,2-Dimethoxyethane;
DMF	*N,N*-Dimethylformamide;
DMSO	Methyl sulfoxide;
DPPA	Diphenylphosphoryl azide;
DTT	Dithiothreitol;
EDC	1-(3-Dimethylaminopropyl)-3-ethyl-carbodiimide-hydrochloride;
EDTA	Ethylenediaminetetraacetic acid;
ELSD	Evaporative Light Scattering Detector;
ES	Electrospray;
ESI	Electrospray ionization;
Et_2O	Diethyl ether;
Et_3N	Triethylamine;
EtOAc	Ethyl acetate;
EtOH	Ethanol;
FAB	Fast Atom Bombardment;
HEPES	4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid;
HMPA	Hexamethylphosphoramide;
HOAc	Acetic acid;
HOBt	1-Hydroxybenzotriazole hydrate;
HOOBt	3-Hydroxy-1,2,2-benzotriazin-4(3*H*)-one;
HPLC	High-performance liquid chromatography;
HRMS	High Resolution Mass Spectroscopy;
KOtBu	Potassium *tert*-butoxide;
LAH	Lithium aluminum hydride;

LCMS	Liquid Chromatography Mass Spectroscopy;
MCPBA	*m*-Chloroperoxybenzoic acid;
Me	Methyl;
MeOH	Methanol;
MP-Carbonate	Macroporous polystyrene carbonate;
Ms	Methanesulfonyl;
MS	Mass Spectroscopy;
MsCl	Methanesulfonyl chloride;
n-Bu	*n*-butyl;
n-Bu_3P	Tri-*n*-butylphosphine;
NaHMDS	Sodium bis(trimethylsilyl)amide;
NBS	*N*-Bromosuccinimide;
NMM	N-methylmorpholine;
NMR	Nuclear Magnetic Resonance;
$Pd(PPh_3)_4$	Palladium tetrakis(triphenylphosphine);
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium (0);
Ph	phenyl;
PMSF	α-Toluenesulfonyl fluoride;
PS-DCC	Polystyrene dicyclohexylcarbodiimide;
PS-DMAP	Polystyrene dimethylaminopyridine;
PS-NMM	Polystyrene *N*-methylmorpholine;
Py or pyr	Pyridine;
PYBOP (or PyBOP)	Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate;
RPLC	Reverse Phase Liquid Chromatography;
RT	Room Temperature;
SCX SPE	Strong Cation Exchange Solid Phase Extraction;
t-Bu	*tert*-Butyl;
TBAF	Tetrabutylammonium fluoride;
TBSCl	*tert*-Butyldimethylsilyl chloride;
TFA	Trifluoroacetic acid;
THF	Tetrahydrofuran;
TIPS	Triisopropylsilyl;
TMS	Tetramethylsilane; and
Tr	Trityl.

UTILITY

In another aspect, this present invention relates to a method of modulating the catalytic activity of PKs (protein kinases) in a mammal in need thereof comprising contacting the PK with a compound of Formula I.

As used herein, the term "modulation" or "modulating" refers to the alteration of the catalytic activity of receptor tyrosine kinases (RTKs), cellular tyrosine kinases (CTKs)and serine-threonine kinases (STKs). In particular, modulating refers to the activation of the catalytic activity of RTKs, CTKs and STKs, preferably the activation or inhibition of the catalytic activity of RTKs, CTKs and STKs, depending on the concentration of the compound or salt to which the RTKs, CTKs or STKs is exposed or, more preferably, the inhibition of the catalytic activity of RTKs, CTKs and STKs.

The term "catalytic activity" as used herein refers to the rate of phosphorylation of tyrosine under the influence, direct or indirect, of RTKs and/or CTKs or the phosphorylation of serine and threonine under the influence, direct or indirect, of STKs.

The term "contacting" as used herein refers to bringing a compound of this invention and a target PK together in such a manner that the compound can affect the catalytic activity of the PK, either directly; i.e., by interacting with the kinase itself, or indirectly; i.e., by interacting with another molecule on which the catalytic activity of the kinase is dependent. Such "contacting" can be accomplished "*in vitro,*" i.e., in a test tube, a petri dish or the like. In a test tube, contacting may involve only a compound and a PK of interest or it may involve whole cells. Cells may also be maintained or grown in cell culture dishes and contacted with a compound in that environment. In this context, the ability of a particular compound to affect a PK related disorder; i.e., the IC_{50} of the compound, defined below, can be determined before use of the compounds *in vivo* with more complex living organisms is attempted. For cells outside the organism, multiple methods exist, and are well known to those skilled in the art, to get the PKs in contact with the compounds including, but not limited to, direct cell microinjection and numerous transmembrane carrier techniques.

The above-referenced PK is selected from the group comprising an RTK, a CTK or an STK in another aspect of this invention. Preferably, the PK is an RTK.

Furthermore, it is an aspect of this invention that the receptor tyrosine kinase (RTK) whose catalytic activity is modulated by a compound of this invention is selected from the group comprising EGF, HER2, HER3, HER4, IR, IGF-1R, IRR, PDGFRα, PDGFRβ, TrkA, TrkB, TrkC, HGF, CSFIR, C-Kit, C-fms, Flk-1R, Flk4, KDR/Flk-1, Flt-1,

FGFR-1R, FGFR-1R, FGFR-3R and FGFR-4R. Preferably, the RTK is preferably, the receptor protein kinase is selected from IR, IGF-1R, or IRR.

In addition, it is an aspect of this invention that the cellular tyrosine kinase whose catalytic activity is modulated by a compound of this invention is selected from the group consisting of Src, Frk, Btk, Csk, Abl, ZAP70, Fes, Fps, Fak, Jak, Ack, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk.

Another aspect of this invention is that the serine-threonine protein kinase whose catalytic activity is modulated by a compound of this invention is selected from the group consisting of CDK2 and Raf.

In another aspect, this invention relates to a method for treating or preventing a PK-related disorder in a mammal in need of such treatment comprising administering to the mammal a therapeutically effective amount of one or more of the compounds described above.

As used herein, "PK-related disorder," "PK driven disorder," and "abnormal PK activity" all refer to a condition characterized by inappropriate (i.e., diminished or, more commonly, exessive) PK catalytic activity, where the particular PK can be an RTK, a CTK or an STK. Inappropriate catalytic activity can arise as the result of either: (1) PK expression in cells which normally do not express PKs; (2) increased PK expression leading to unwanted cell proliferation, differentiation and/or growth; or, (3) decreased PK expression leading to unwanted reductions in cell proliferation, differentiation and/or growth. Excessive-activity of a PK refers to either amplification of the gene encoding a particular PK or its ligand, or production of a level of PK activity which can correlate with a cell proliferation, differentiation and/or growth disorder (that is, as the level of the PK increases, the severity of one or more symptoms of a cellular disorder increase as the level of the PK activity decreases).

"Treat," "treating" or "treatment" with regard to a PK-related disorder refers to alleviating or abrogating the cause and/or the effects of a PK-related disorder.

As used herein, the terms "prevent", "preventing" and "prevention" refer to a method for barring a mammal from acquiring a PK-related disorder in the first place.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each

understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The term “treating cancer” or “treatment of cancer” refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

The protein kinase-related disorder may be selected from the group comprising an RTK, a CTK or an STK-related disorder in a further aspect of this invention. Preferably, the protein kinase-related disorder is an RTK-related disorder.

In yet another aspect of this invention, the above referenced PK-related disorder may be selected from the group consisting of an EGFR-related disorder, a PDGFR-related disorder, an IGFR-related disorder and a flk-related disorder.

The above referenced PK-related disorder may be a cancer selected from, but not limited to, astrocytoma, basal or squamous cell carcinoma, brain cancer, gliobastoma, bladder cancer, breast cancer, colorectal cancer, chrondrosarcoma, cervical cancer, adrenal cancer, choriocarcinoma, esophageal cancer, endometrial carcinoma, erythroleukemia, Ewing’s sarcoma, gastrointestinal cancer, head and neck cancer, hepatoma, glioma, hepatocellular carcinoma, leukemia, leiomyoma, melanoma, non-small cell lung cancer, neural cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, rhabdomyosarcoma, small cell lung cancer, thyoma, thyroid cancer, testicular cancer and osteosarcoma in a further aspect of this invention. More preferably, the PK-related disorder is a cancer selected from brain cancer, breast cancer, prostate cancer, colorectal cancer, small cell lung cancer, non-small cell lung cancer, renal cell carcinoma or endometrial carcinoma.

Included within the scope of the present invention is a pharmaceutical composition, which is comprised of a compound of Formula I as described above and a pharmaceutically acceptable carrier. The present invention also encompasses a method of treating or preventing cancer in a mammal in need of such treatment which is comprised of administering to said mammal a therapeutically effective amount of a compound of Formula I. Types of cancers which may be treated using compounds of Formula I include, but are not limited to, astrocytoma, basal or squamous cell carcinoma, brain cancer, gliobastoma, bladder cancer, breast cancer, colorectal cancer, chrondrosarcoma, cervical cancer, adrenal

cancer, choriocarcinoma, esophageal cancer, endometrial carcinoma, erythroleukemia, Ewing's sarcoma, gastrointestinal cancer, head and neck cancer, hepatoma, glioma, hepatocellular carcinoma, leukemia, leiomyona, melanoma, non-small cell lung cancer, neural cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, rhabdomyosarcoma, small cell lung cancer, thymona, thyroid cancer, testicular cancer and osteosarcoma in a further aspect of this invention. More preferably, the cancer being treated is selected from breast cancer, prostate cancer, colorectal cancer, small cell lung cancer, non-small cell lung cancer, renal cell carcinoma, or endometrial carcinoma.

The above-referenced PK-related disorder may be an IGFR-related disorder selected from diabetes, an autoimmune disorder, Alzheimer's and other cognitive disorders, a hyperproliferation disorder, aging, cancer, acromegaly, Crohn's disease, endometriosis, diabetic retinopathy, restenosis, fibrosis, psoriasis, osteoarthritis, rheumatoid arthritis, an inflammatory disorder and angiogenesis in yet another aspect of this invention.

A method of treating or preventing retinal vascularization which is comprised of administering to a mammal in need of such treatment a therapeutically effective amount of compound of Formula I is also encompassed by the present invention. Methods of treating or preventing ocular diseases, such as diabetic retinopathy and age-related macular degeneration, are also part of the invention.

Also included within the scope of the present invention is a method of treating or preventing inflammatory diseases, such as rheumatoid arthritis, psoriasis, contact dermatitis and delayed hypersensitivity reactions, as well as treatment or prevention of bone associated pathologies selected from osteosarcoma, osteoarthritis, and rickets.

Other disorders which might be treated with compounds of this invention include, without limitation, immunological and cardiovascular disorders such as atherosclerosis.

Thus, the scope of the instant invention encompasses the use of the instantly claimed compounds in combination with a second compound selected from:

1) an estrogen receptor modulator,
2) an androgen receptor modulator,
3) retinoid receptor modulator,
4) a cytotoxic/cytostatic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,

8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor,
10) an angiogenesis inhibitor,
11) a PPAR-γ agonists,
12) a PPAR-δ agonists,
13) an inhibitor of inherent multidrug resistance,
14) an anti-emetic agent,
15) an agent useful in the treatment of anemia,
16) an agent useful in the treatment of neutropenia,
17) an immunologic-enhancing drug,
18) an inhibitor of cell proliferation and survival signaling, and
19) an agent that interferes with a cell cycle checkpoint.

In an embodiment, the angiogenesis inhibitor to be used as the second compound is selected from a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP (matrix metalloprotease) inhibitor, an integrin blocker, interferon-α, interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, or an antibody to VEGF. In an embodiment, the estrogen receptor modulator is tamoxifen or raloxifene.

Also included in the scope of the claims is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with radiation therapy and/or in combination with a compound selected from:

1) an estrogen receptor modulator,
2) an androgen receptor modulator,
3) a retinoid receptor modulator,
4) a cytotoxic/cytostatic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor,
10) an angiogenesis inhibitor,
11) PPAR-γ agonists,
12) PPAR-δ agonists,

13) an inhibitor of inherent multidrug resistance,
14) an anti-emetic agent,
15) an agent useful in the treatment of anemia,
16) an agent useful in the treatment of neutropenia,
17) an immunologic-enhancing drug,
18) an inhibitor of cell proliferation and survival signaling, and
19) an agent that interferes with a cell cycle checkpoint.

And yet another embodiment of the invention is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with paclitaxel or trastuzumab.

The invention further encompasses a method of treating or preventing cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with a COX-2 inhibitor.

The instant invention also includes a pharmaceutical composition useful for treating or preventing cancer that comprises a therapeutically effective amount of a compound of Formula I and a compound selected from:

1) an estrogen receptor modulator,
2) an androgen receptor modulator,
3) a retinoid receptor modulator,
4) a cytotoxic/cytostatic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor,
10) an angiogenesis inhibitor,
11) a PPAR-γ agonist,
12) a PPAR-δ agonists,
13) an inhibitor of cell proliferation and survival signaling, and
14) an agent that interferes with a cell cycle checkpoint.

And yet another embodiment is the method of treating cancer using the combination discussed above, in combination with radiation therapy.

And yet another embodiment of the invention is a method of treating cancer which comprises administering a therapeutically effective amount of a compound of Formula I in combination with paclitaxel or trastuzumab. The PKs whose catalytic activity is

modulated by the compounds of this invention include protein tyrosine kinases of which there are two types, receptor tyrosine kinases (RTKs) and cellular tyrosine kinases (CTKs), and serine-threonine kinases (STKs). RTK-mediated signal transduction, is initiated by extracellular interaction with a specific growth factor (ligand), followed by receptor dimerization (or conformational changes in the case of IR, IGF-1R or IRR), transient stimulation of the intrinsic protein tyrosine kinase activity, autophosphorylation and subsequent phosphorylation of other substrate proteins. Binding sites are thereby created for intracellular signal transduction molecules and lead to the formation of complexes with a spectrum of cytoplasmic signaling molecules that facilitate the appropriate cellular response (e.g., cell division, metabolic effects on the extracellular microenvironment, etc.). See Schlessinger and Ullrich, 1992, Neuron 9:303-391.

It has been shown that tyrosine phosphorylation sites, on growth factor receptors, function as high-affinity binding sites for SH2 (src homology) domains of signaling molecules. Fantl et al., 1992, Cell 69:413-423; Songyang et al., 1994, Mol., Cell. Biol. 14:2777-2785); Songyang et al., 1993, Cell 72:767-778; and Koch et al., 1991, Science 252:668-678. Another signaling molecule domain, which interacts with phosphorylated tyrosines, is termed a PTB domain. Blaikie et al., 1994, J. Biol. Chem. 269:32031-32034; Gustafson et al., 1995, Mol. Cell Biol., 15:2500-25008; Kavanaugh and Williams, 1994, Science 266:1862-1865. Several intracellular substrate proteins that associate with RTKs have been identified. They may be divided into two principal groups: (1) substrates which have a catalytic domain; and (2) substrates which lack such domain, but which serve as adapters and associate with catalytically active molecules. Songyang et al., 1993, Cell 72:767-778. The specificity of the interactions between receptors and SH2 domains of their substrates is determined by the amino acid residues immediately surrounding the phosphorylated tyrosine residue. Differences in the binding affinities between SH2 or PTB domains and the amino acid sequences surrounding the phosphotyrosine residues on particular receptors are consistent with the observed differences in their substrate phosphorylation profiles. Songyang et al., 1993, Cell 72:767-778. These observations suggest that the function of each RTK is determined not only by its pattern of expression and ligand availability, but also by the array of downstream signal transduction pathways that are activated by a particular receptor. Thus, phosphorylation provides an important regulatory step, which determines the selectivity of signaling pathways recruited by specific growth factor receptors, as well as differentiation factor receptors.

STKs, being primarily cytosolic, affect the internal biochemistry of the cell, often as a down-stream response to a PTK event. STKs have been implicated in the signaling process which initiates DNA synthesis and subsequent mitosis leading to cell proliferation.

Thus, PK signal transduction results in, among other responses, cell proliferation, differentiation, growth, metabolism, and cellular mobility. Abnormal cell proliferation may result in a wide array of disorders and diseases, including the development of neoplasia such as carcinoma, sarcoma, glioblastoma and hemangioma, disorders such as leukemia, psoriasis, arteriosclerosis, arthritis and diabetic retinopathy and other disorders related to uncontrolled angiogenesis and/or vasculogenesis.

A precise understanding of the mechanism by which the compounds of this invention inhibit PKs is not required in order to practice the present invention. However, while not hereby being bound to any particular mechanism or theory, it is believed that the compounds interact with the amino acids in the catalytic region of PKs. PKs typically possess a bi-lobate structure wherein ATP appears to bind in the cleft between the two lobes in a region where the amino acids are conserved among PKs. Inhibitors of PKs are believed to bind by non-covalent interactions such as hydrogen bonding, van der Waals forces and ionic interactions in the same general region where the aforesaid ATP binds to the PKs. The compounds disclosed herein may have utility as *in vitro* assays for such proteins as well as exhibiting *in vivo* therapeutic effects through interaction with such proteins.

In another aspect, the protein kinase (PK), the catalytic activity of which is modulated by contact with a compound of this invention, is a protein tyrosine kinase (PTK), more particularly, a receptor protein tyrosine kinase (RTK). Among the RTKs whose catalytic activity can be modulated with a compound of this invention, or salt thereof, are, without limitation, EGF, HER2, HER3, HER4, IR, IGF-1R, IRR, PDGFRα, PDGFRβ, TrkA, TrkB, TrkC, HGF, CSFIR, C-Kit, C-fms, Flk-1R, Flk4, KDR/Flk-1, Flt-1, FGFR-1R, FGFR-2R, FGFR-3R and FGFR-4R. Most preferably, the RTK is selected from IGF-1R.

The protein tyrosine kinase whose catalytic activity is modulated by contact with a compound of this invention, or a salt or a prodrug thereof, can also be a non-receptor or cellular protein tyrosine kinase (CTK). Thus, the catalytic activity of CTKs such as, without limitation, Src, Frk, Btk, Csk, Abl, ZAP70, Fes, Fps, Fak, Jak, Ack, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk, may be modulated by contact with a compound or salt of this invention.

Still another group of PKs which may have their catalytic activity modulated by contact with a compound of this invention are the serine-threonine protein kinases such as, without limitation, CDK2 and Raf.

This invention is also directed to compounds that modulate PK signal transduction by affecting the enzymatic activity of RTKs, CTKs and/or STKs, thereby interfering with the signals transduced by such proteins. More particularly, the present invention is directed to compounds which modulate RTK, CTK and/or STK mediated signal transduction pathways as a therapeutic approach to cure many kinds of solid tumors, including, but not limited to, carcinomas, sarcomas including Kaposi's sarcoma, erythroblastoma, glioblastoma, meningioma, astrocytoma, melonoma and myoblastoma. Treatment or prevention of non-solid tumor cancers such as leukemia are also contemplated by this invention. Indications may include, but are not limited to brain cancers, bladder cancers, ovarian cancers, gastric cancers, pancreatic cancers, colon cancers, blood cancers, breast cancers, prostrate cancers, renal cell carcinomas, lung cancer and bone cancers.

Further examples, without limitation, of the types of disorders related to inappropriate PK activity that the compounds described herein may be useful in preventing, treating and studying, are cell proliferative disorders, fibrotic disorders and metabolic disorders.

As previously mentioned, the Insulin-like Growth Factor-1 Receptor (IGF-1R) belongs to the family of transmembrane tyrosine kinase receptors such as platelet-derived growth factor receptor, the epidermal growth factor receptor, and the insulin receptor. There are two known ligands for the IGF-1R receptor. They are IGF-1 and IGF-2. As used herein, the term "IGF" refers to both IGF-1 and IGF-2. The insulin-like growth factor family of ligands, receptors and binding proteins is reviewed in Krywicki and Yee, *Breast Cancer Research and Treatment*, 22:7-19, 1992.

IGF/IGF-1R driven disorders are characterized by inappropriate or over-activity of IGF/IGF-1R. Inappropriate IGF activity refers to either: (1) IGF or IGF-1R expression in cells which normally do not express IGF or IGF-1R;
(2) increased IGF or IGF-1R expression leading to unwanted cell proliferation such as cancer; (3) increased IGF or IGF-1R activity leading to unwanted cell proliferation, such as cancer; and/or over-activity of IGF or IGF-1R. Over-activity of IGF or IGF-1R refers to either an amplification of the gene encoding IGF-1, IGF-2, IGF-1R or the production of a level of IGF activity which can be correlated with a cell proliferative disorder (i.e., as the level of IGF increases the severity of one or more of the symptoms of the cell proliferative disorder increases) the bioavailability of IGF-1 and IGF-2 can also be affected by the presence or absence of a set of IGF binding presence or absence of a set of IGF binding proteins (IGF BPs) of which there are six know. Over activity of IGF/IGF-1R can also result from a down regulation of IGF-2 which contains an IGF-2 binding domain, but no

intracellular kinase domain. Examples of IGF/IGF-1R driven disorders include the various IGF/IGF-1R related human malignancies reviewed in Cullen, *et al.*, *Cancer Investigation*, 9(4):443-454, 1991, incorporated herein by reference in its entirety, including any drawings. IGF/IGF-1Rs clinical importance and role in regulating osteoblast function is reviewed in Schmid, *Journal of Internal Medicine*, 234:535-542, 1993.

Thus, IGF-1R activities include: (1) phosphorylation of IGF-1R protein; (2) phosphorylation of an IGF-1R protein substrate; (3) interaction with an IGF adapter protein; (4) IGF-1R protein surface expression. Additional IGF-1R protein activities can be identified using standard techniques. IGF-1R activity can be assayed by measuring one or more of the following activities: (1) phosphorylation of IGF-1R; (2) phosphorylation of an IGF-1R substrate; (3) activation of an IGF-1R adapter molecule; and (4) activation of downstream signaling molecules, and/or (5) increased cell division. These activities can be measured using techniques described below and known in the arts.

IGF-1R has been implicated as an absolute requirement for the establishment and maintenance of the transformed phenotype both *in vitro* and *in vivo* in several cell types (R. Baserga, *Cancer Research* 55:249-252, 1995). Herbimycin A has been said to inhibit the IGF-1R protein tyrosine kinase and cellular proliferation in human breast cancer cells (Sepp-Lorenzino, et al., 1994, *J. Cell Biochem. Suppl.* 18b: 246). Experiments studying the role of IGF-1R in transformation have used antisense strategies, dominant negative mutants, and antibodies to the IGF-1R and have led to the suggestion that IGF-1R may be a preferred target for therapeutic interventions.

IGF-1R, in addition to being implicated in nutritional support and in type-II diabetes, has also been associated with several types of cancers. For example, IGF-1 has been implicated as an autocrine growth stimulator for several tumor types, e.g. human breast cancer carcinoma cells (Arteago et al., J. Clin. Invest., 1989, 84:1418-1423) and small lung tumor cells (Macauley et al., Cancer Res., 1989, 50:2511-2517). In addition, IGF-1, while integrally involved in the normal growth and differentiation of the nervous system, also appears to be an autocrine stimulator of human gliomas. Sandberg-Nordqvist et al., Cancer Res., 1993, 53:2475-2478.

An example of IGF-2's protential involvement in colorectal cancer may be found in the up-regulation of IGF-2 mRNA in colon tumors relative to normal colon tissue. (Zhang et al., Science (1997) 276:1268-1272.) IGF-2 may also play a role in hypoxia induced neovascularization of tumors. (Minet et al., Int. J. Mol. Med. (2000) 5:253-259.) IGF-2 may also play a role in tumorigenesis through activation of an insulin receptor isoform-A. IGF-2 activation of insulin receptor isoform-A activates cell survival signaling

pathways in cells but its relative contribution to tumor cell growth and survival is unknown at this time. Insulin receptor isoform-A's kinase domain is identical to the standard insulin receptor's. Scalia et al., 2001, J. Cell Biochem. 82:610-618.

The importance of IGF-1R and its ligands in cell types in culture (fibroblasts, epithelial cells, smooth muscle cells, T-lymphocytes, myeloid cells, chondrocytes and osteoblasts (the stem cells of the bone marrow)) is illustrated by the ability of IGF-1 to stimulate cell growth and proliferation. Goldring and Goldring, Eukaryotic Gene Expression, 1991, 1:301-326. In a series of recent publications, Baserga and others suggests that IGF-1R plays a central role in the mechanism of transformation and, as such, could be a preferred target for therapeutic interventions for a broad spectrum of human malignancies. Baserga, Cancer Res., 1995, 55:249-252; Baserga, Cell, 1994, 79:927-930; Coppola et al., Mol. Cell. Biol., 1994, 14:4588-4595; Baserga, Trends in Biotechnology, 1996, 14:150-152; H.M. Khandwala et al., Endocrine Reviews, 21:215-244, 2000. The predominant cancers that may be treated using a compound of the instant invention include, but are not limited to breast cancer, prostate cancer, colorectal cancer, small cell lung cancer, non-small cell lung cancer, renal cell carcinoma, or endometrial carcinoma.

IGF-1 has also been associated with retinal neovascularization. Proliferative diabetes retinopathy has been seen in some patients having high levels of IGF-1. (L.E. Smith et al., Nature Medicine, 1999, 5:1390-1395.)

Compounds of the instant invention may also be useful as anti-aging agents. It has been observed that there is a link between IGF signalling and aging. Experiments have shown that calorie-restricted mammals have low levels of insulin and IGF-1 and have a longer life span. Similar observations have been made for insects as well. (See C. Kenyon, Cell, 2001, 105:165-168; E. Strauss, Science, 2001, 292:41-43; K.D. Kimura et al., Science 1997, 277:942-946; M. Tatar et al., Science, 2001, 292:107-110).

STKs have been implicated in many types of cancer including, notably, breast cancer (Cance et al., Int. J. Cancer, 1993, 54:571-77).

The association between abnormal PK activity and disease is not restricted to cancer. For example, RTKs have been associated with diseases such as psoriasis, diabetes mellitus, endometriosis, angiogenesis, atheromatous plaque development, Alzheimer's disease, epidermal hyperproliferation, neurodegenerative diseases, age-related macular degeneration and hemangiomas. For example, EGFR has been indicated in corneal and dermal wound healing. Defects in Insulin-R and IGF-1R are indicated in type-II diabetes mellitus. A more complete correlation between specific RTKs and their therapeutic indications is set forth in Plowman et al., DN&P, 1994, 7:334-339.

As noted previously, not only RTKs but CTKs including, but not limited to, src, abl, fps, yes, fyn, lyn, lck, Zap70, blk, hck, fgr and yrk (reviewed by Bolen et al., FASEB J., 1993, 6:3403-3409) are involved in the proliferative and metabolic signal transduction pathway and thus could be expected, and have been shown, to be involved in many PTK-mediated disorders to which the present invention is directed. For example, mutated src (v-src) has been shown to be an oncoprotein ($pp60^{v\text{-}src}$) in chicken. Moreover, its cellular homolog, the protooncogene $pp60^{c\text{-}src}$ transmits oncogenic signals of many receptors. Over-expression of EGFR or HER2/neu in tumors leads to the constitutive activation of $pp60^{c\text{-}src}$, which is characteristic of malignant cells, but absent in normal cells. On the other hand, mice deficient in the expression of c-src exhibit an osteopetrotic phenotype, indicating a key participation of c-src in osteoclast function and a possible involvement in related disorders.

Similarly, Zap70 has been implicated in T-cell signaling which may relate to autoimmune disorders.

STKs have been associated with inflammation, autoimmune disease, immunoresponses, and hyperproliferation disorders such as restenosis, fibrosis, psoriasis, osteoarthritis and rheumatoid arthritis.

PKs have also been implicated in embryo implantation. Thus, the compounds of this invention may provide an effective method of preventing such embryo implantation and thereby be useful as birth control agents.

Finally, both RTKs and CTKs are currently suspected as being involved in hyperimmune disorders.

These and other aspects of the invention will be apparent from the teachings contained herein.

A method for identifying a chemical compound that modulates the catalytic activity of one or more of the above discussed protein kinases is another aspect of this invention. The method involves contacting cells expressing the desired protein kinase with a compound of this invention (or its salt or prodrug) and monitoring the cells for any effect that the compound has on them. The effect may be any observable, either to the naked eye or through the use of instrumentation, change or absence of change in a cell phenotype. The change or absence of change in the cell phenotype monitored may be, for example, without limitation, a change or absence of change in the catalytic activity of the protein kinase in the cells or a change or absence of change in the interaction of the protein kinase with a natural binding partner.

COMPOSITION

Pharmaceutical compositions of the above compounds are a further aspect of this invention.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's bloodstream by local bolus injection.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients, which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropyl-methylcellulose or hydroxypropyl-cellulose, or a time delay material such as ethyl cellulose, cellulose acetate buryrate may be employed.

The compounds of the instant invention may also be co-administered with other well-known therapeutic agents that are selected for their particular usefulness against

the condition that is being treated. For example, in the case of bone-related disorders, combinations that would be useful include those with antiresorptive bisphosphonates, such as alendronate and risedronate; integrin blockers (defined further below), such as $\alpha_v\beta_3$ antagonists; conjugated estrogens used in hormone replacement therapy, such as PREMPRO®, PREMARIN® and ENDOMETRION®; selective estrogen receptor modulators (SERMs), such as raloxifene, droloxifene, CP-336,156 (Pfizer) and lasofoxifene; cathespin K inhibitors; and ATP proton pump inhibitors.

The instant compounds are also useful in combination with known anti-cancer agents. Such known anti-cancer agents include the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors. The instant compounds are particularly useful when coadminsitered with radiation therapy. The synergistic effects of inhibiting VEGF in combination with radiation therapy have been described in the art. (see WO 00/61186.)

"Estrogen receptor modulators" refers to compounds, which interfere or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

"Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

"Retinoid receptor modulators" refers to compounds, which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N-4-carboxyphenyl retinamide.

"Cytotoxic agents" refer to compounds which cause cell death primarily by interfering directly with the cell's functioning or inhibit or interfere with cell myosis, including alkylating agents, tumor necrosis factors, intercalators, microtubulin inhibitors, and topoisomerase inhibitors.

Examples of cytotoxic agents include, but are not limited to, tirapazimine, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, doxorubicin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine) platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro) platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (see WO 00/50032).

Examples of microtubulin inhibitors include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, and BMS188797.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':b,7]indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydroxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexohydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-

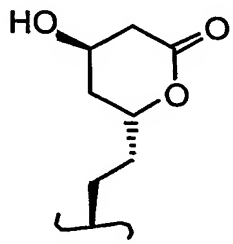
(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c] quinolin-7-one, and dimesna.

"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-flurouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine, and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone. "Antiproliferative agents" also includes monoclonal antibodies to growth factors, other than those listed under "angiogenesis inhibitors", such as trastuzumab, and tumor suppressor genes, such as p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Patent No. 6,069,134, for example).

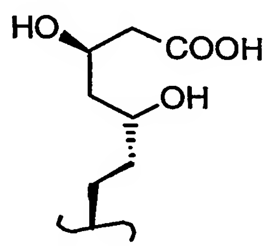
"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33. The terms "HMG-CoA reductase inhibitor" and "inhibitor of HMG-CoA reductase" have the same meaning when used herein.

Examples of HMG-CoA reductase inhibitors that may be used include, but are not limited to, lovastatin (MEVACOR®, see U.S. Patent Nos. 4,231,938, 4,294,926 and 4,319,039); simvastatin (ZOCOR®, see U.S. Patent Nos. 4,444,784, 4,820,850 and 4,916,239); pravastatin (PRAVACHOL®, see U.S. Patent Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589); fluvastatin (LESCOL®, see U.S. Patent Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896); atorvastatin (LIPITOR®, see U.S. Patent Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952); and cerivastatin (also known as rivastatin and BAYCHOL®, see U.S. Patent No. 5,177,080). The structural formulae of these and additional HMG-CoA reductase inhibitors

that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention. An illustration of the lactone portion and its corresponding open-acid form is shown below as structures I and II.



Lactone
I



Open-Acid
II

In HMG-CoA reductase inhibitors where an open-acid form can exist, salt and ester forms may preferably be formed from the open-acid, and all such forms are included within the meaning of the term "HMG-CoA reductase inhibitor" as used herein. Preferably, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin, and most preferably simvastatin. Herein, the term "pharmaceutically acceptable salts" with respect to the HMG-CoA reductase inhibitor shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenz-imidazole, diethylamine, piperazine, and tris(hydroxymethyl) aminomethane. Further examples of salt forms of HMG-CoA reductase inhibitors may include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride,

hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate.

Ester derivatives of the described HMG-CoA reductase inhibitor compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

"Prenyl-protein transferase inhibitor" refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase). Examples of prenyl-protein transferase inhibiting compounds include (±)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl) methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, (-)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, (+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl) methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, 5(S)-n-butyl-1-(2,3-dimethylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, (S)-1-(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl) methyl)-2-piperazinone, 5(S)-n-Butyl-1-(2-methylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, 1-(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-2-piperazinone, 1-(2,2-diphenylethyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl]piperidine, 4-{5-[4-hydroxymethyl-4-(4-chloropyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl} benzonitrile, 4-{5-[4-hydroxymethyl-4-(3-chlorobenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile, 4-{3-[4-(2-oxo-2H-pyridin-1-yl)benzyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-{3-[4-(5-chloro-2-oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-{3-[4-(2-oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl}benzonitrile, 18,19-dihydro-19-oxo-5*H*,17*H*-6,10:12,16-dimetheno-1H-imidazo[4,3-*c*][1,11,4]dioxaazacyclo -nonadecine-9-carbonitrile, (±)-19,20-dihydro-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo[*d*]imidazo[4,3-*k*][1,6,9,12]oxatriaza-cyclooctadecine-9-carbonitrile, 19,20-dihydro-19-oxo-5*H*,17*H*-18,21-ethano-6,10:12,16-dimetheno-22*H*-imidazo[3,4-*h*][1,8,11,14]oxatriazacycloeicosine-9-carbonitrile, and (±)-19,20-dihydro-3-methyl-19-oxo-

5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo [*d*]imidazo[4,3-*k*][1,6,9,12]oxa-triazacyclooctadecine-9-carbonitrile.

Other examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U.S. Patent No. 5,420,245, U.S. Patent No. 5,523,430, U.S. Patent No. 5,532,359, U.S. Patent No. 5,510,510, U.S. Patent No. 5,589,485, U.S. Patent No. 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Patent No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Patent No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Patent No. 5,532,359. For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see European J. of Cancer, Vol. 35, No. 9, pp.1394-1401 (1999).

Examples of HIV protease inhibitors include amprenavir, abacavir, CGP-73547, CGP-61755, DMP-450, indinavir, nelfinavir, tipranavir, ritonavir, saquinavir, ABT-378, AG 1776, and BMS-232,632. Examples of reverse transcriptase inhibitors include delaviridine, efavirenz, GS-840, HB Y097, lamivudine, nevirapine, AZT, 3TC, ddC, and ddI.

"Angiogenesis inhibitors" refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR20), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon-α, interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxygenase-2 inhibitors like celecoxib and rofecoxib (PNAS, Vol. 89, p. 7384 (1992); JNCI, Vol. 69, p. 475 (1982); Arch. Opthalmol., Vol. 108, p.573 (1990); Anat. Rec., Vol. 238, p. 68 (1994); FEBS Letters, Vol. 372, p. 83 (1995); Clin, Orthop. Vol. 313, p. 76 (1995); J. Mol. Endocrinol., Vol. 16, p.107 (1996); Jpn. J. Pharmacol., Vol. 75, p. 105 (1997); Cancer Res., Vol. 57, p. 1625 (1997); Cell, Vol. 93, p.

705 (1998); Intl. J. Mol. Med., Vol. 2, p. 715 (1998); J. Biol. Chem., Vol. 274, p. 9116 (1999)), carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez *et al.*, J. Lab. Clin. Med. 105:141-145 (1985)), and antibodies to VEGF. (see, Nature Biotechnology, Vol. 17, pp.963-968 (October 1999); Kim *et al.*, Nature, *362*, 841-844 (1993); WO 00/44777; and WO 00/61186).

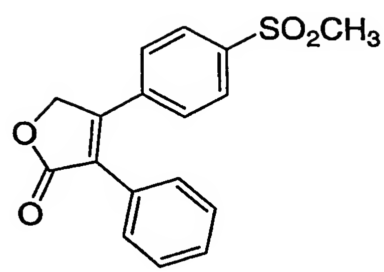
As described above, the combinations with NSAID's are directed to the use of NSAID's which are potent COX-2 inhibiting agents. For purposes of this specification an NSAID is potent if it possess an IC_{50} for the inhibition of COX-2 of 1μM or less as measured by the cell or microsomal assay disclosed herein.

The invention also encompasses combinations with NSAID's which are selective COX-2 inhibitors. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC_{50} for COX-2 over IC_{50} for COX-1 evaluated by the cell or microsomal assay disclosed hereinunder. Such compounds include, but are not limited to those disclosed in

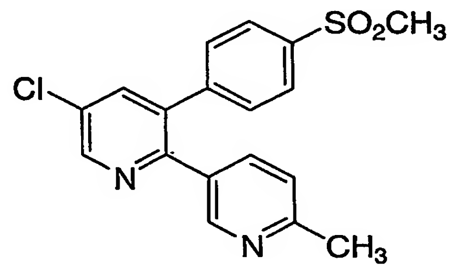
U.S. 5,474,995, issued December 12, 1995, U.S. 5,861,419, issued January 19, 1999, U.S. 6,001,843, issued December 14, 1999, U.S. 6,020,343, issued February 1, 2000, U.S. 5,409,944, issued April 25, 1995, U.S. 5,436,265, issued July 25, 1995, U.S. 5,536,752, issued July 16, 1996, U.S. 5,550,142, issued August 27, 1996, U.S. 5,604,260, issued February 18, 1997, U.S. 5,698,584, issued December 16, 1997, U.S. 5,710,140, issued January 20,1998, WO 94/15932, published July 21, 1994, U.S. 5,344,991, issued June 6, 1994, U.S. 5,134,142, issued July 28, 1992, U.S. 5,380,738, issued January 10, 1995, U.S. 5,393,790, issued February 20, 1995, U.S. 5,466,823, issued November 14, 1995, U.S. 5,633,272, issued May 27, 1997, and U.S. 5,932,598, issued August 3, 1999, all of which are hereby incorporated by reference.

Inhibitors of COX-2 that are particularly useful in the instant method of treatment are:

3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone; and



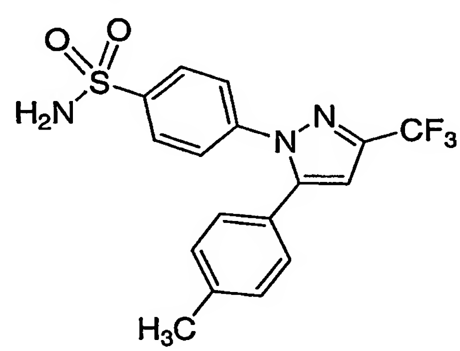
5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine;

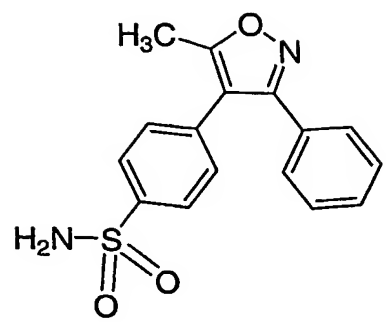


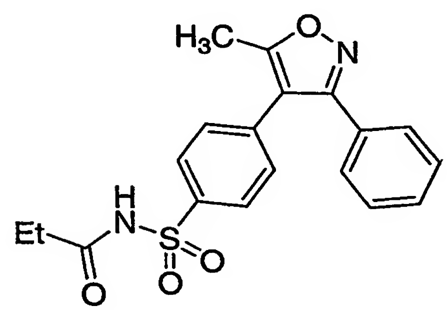
or a pharmaceutically acceptable salt thereof.

General and specific synthetic procedures for the preparation of the COX-2 inhibitor compounds described above are found in U.S. Patent No. 5,474,995, issued December 12, 1995, U.S. Patent No. 5,861,419, issued January 19, 1999, and U.S. Patent No. 6,001,843, issued December 14, 1999, all of which are herein incorporated by reference.

Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to, the following:







or a pharmaceutically acceptable salt thereof.

Compounds, which are described as specific inhibitors of COX-2 and are therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference: WO 94/15932, published July 21, 1994, U.S. Patent No. 5,344,991, issued June 6, 1994, U.S. Patent No. 5,134,142, issued July 28, 1992, U.S. Patent No. 5,380,738, issued January 10, 1995, U.S. Patent No. 5,393,790, issued February 20, 1995, U.S. Patent No. 5,466,823, issued November 14, 1995, U.S. Patent No. 5,633,272, issued May 27, 1997, and U.S. Patent No. 5,932,598, issued August 3, 1999.

Compounds which are specific inhibitors of COX-2 and are therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference: U.S. Patent No. 5,474,995 issued December 12, 1995, U.S. Patent No. 5,861,419 issued January 19, 1999, U.S. Patent No. 6,001,843 issued December 14, 1999, U.S. Patent No. 6,020,343 issued February 1, 2000, U.S. Patent No. 5,409,944 issued April 25, 1995, U.S. Patent No. 5,436,265 issued July 25, 1995, U.S. Patent No. 5,536,752 issued July 16, 1996, U.S. Patent No. 5,550,142 issued August 27, 1996, U.S. Patent No. 5,604,260 issued February 18, 1997, U.S. Patent No. 5,698,584 issued December 16, 1997, and U.S. Patent No. 5,710,140 issued January 20,1998.

Other examples of angiogenesis inhibitors include, but are not limited to, endostation, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide,CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-pyrrolocarbonyl-imino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha v\beta 5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha v\beta_6$, $\alpha v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha v\beta_3$, $\alpha v\beta_5$, $\alpha v\beta_6$, $\alpha v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins.

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl)indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, STI571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

The instant compounds are also useful, alone or in combination with platelet fibrinogen receptor (GP IIb/IIIa) antagonists, such as tirofiban, to inhibit metastasis of cancerous cells. Tumor cells can activate platelets largely via thrombin generation. This activation is associated with the release of VEGF. The release of VEGF enhances metastasis by increasing extravasation at points of adhesion to vascular endothelium (Amirkhosravi, *Platelets* 10, 285-292, 1999). Therefore, the present compounds can serve to inhibit metastasis, alone or in combination with GP IIb/IIIa) antagonists. Examples of other

fibrinogen receptor antagonists include abciximab, eptifibatide, sibrafiban, lamifiban, lotrafiban, cromofiban, and CT50352.

FORMULATIONS

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers, excipients or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and/or topical routes of administration.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

For oral use of a compound according to this invention, particularly for chemotherapy, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and cornstarch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose,

hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or morepreservatives, for example ethyl, or

n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsion. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous solution. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulation.

The injectable solutions or microemulsions may be introduced into a patient's bloodstream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents, which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of Formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

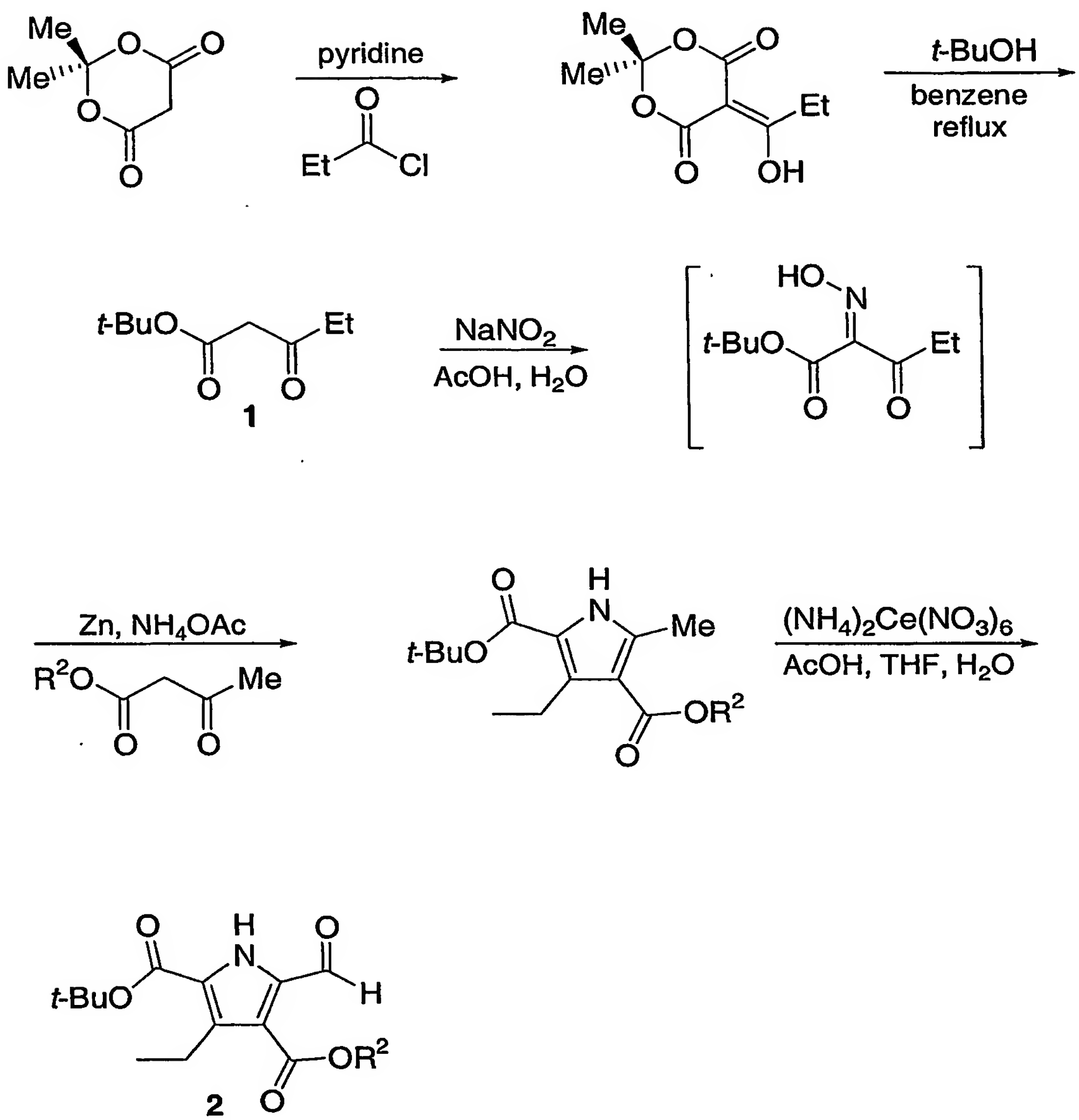
When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

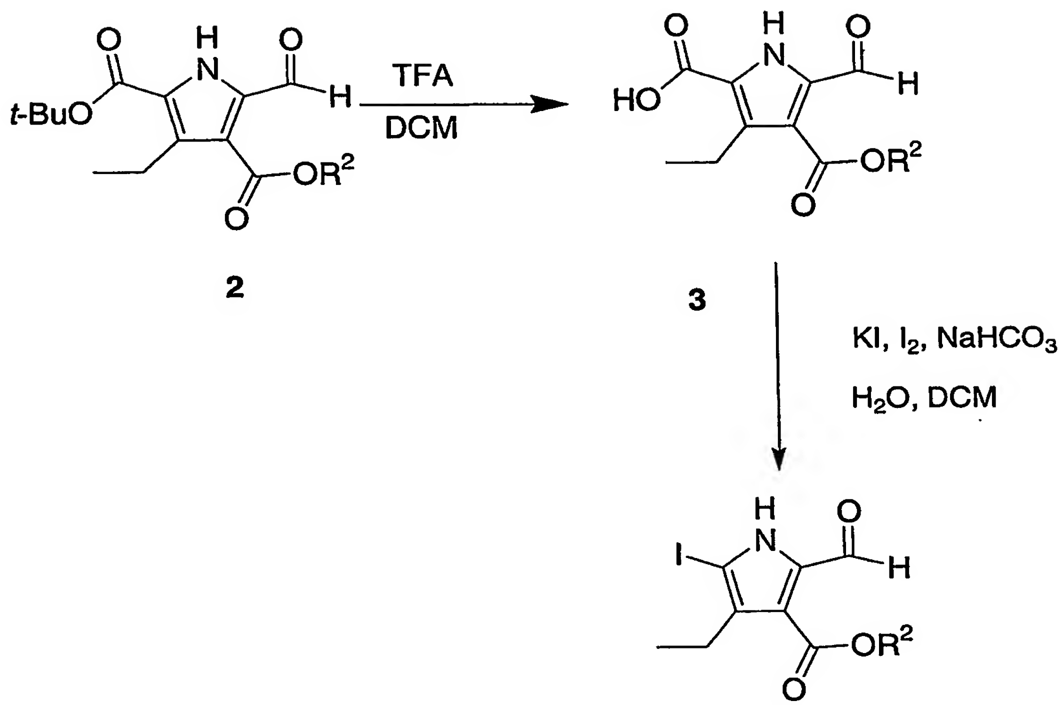
The compounds of this invention may be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. These schemes, therefore, are not limited by the compounds listed nor by any particular substituents employed for illustrative purposes. Substituent numbering, as shown in the schemes, does not necessarily correlate to that used in the claims.

Scheme 1 details the synthesis of pyrrole **2**. The illustrated synthesis of the required beta-ketoester intermediate **1** utilizes the method of Yonemitsu, et al. (JOC (1978) Vol. 43, 2087-2088).

SCHEME 1

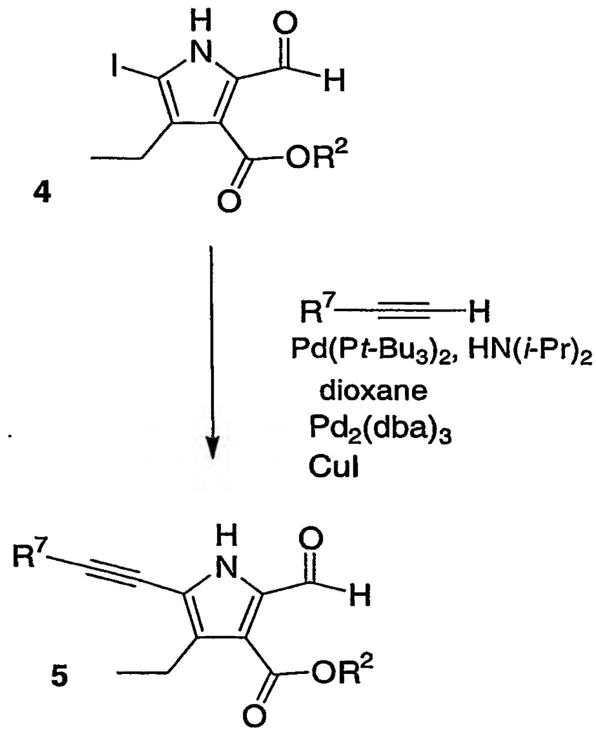

pyridine
t-BuOH
benzene
reflux
NaNO2
AcOH, H2O
Zn, NH4OAc
(NH4)2Ce(NO3)6
AcOH, THF, H2O
1
2

SCHEME 2

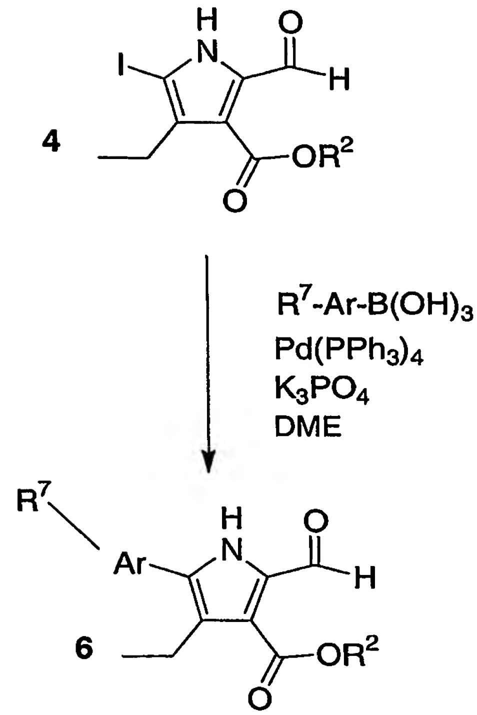


2 3 4

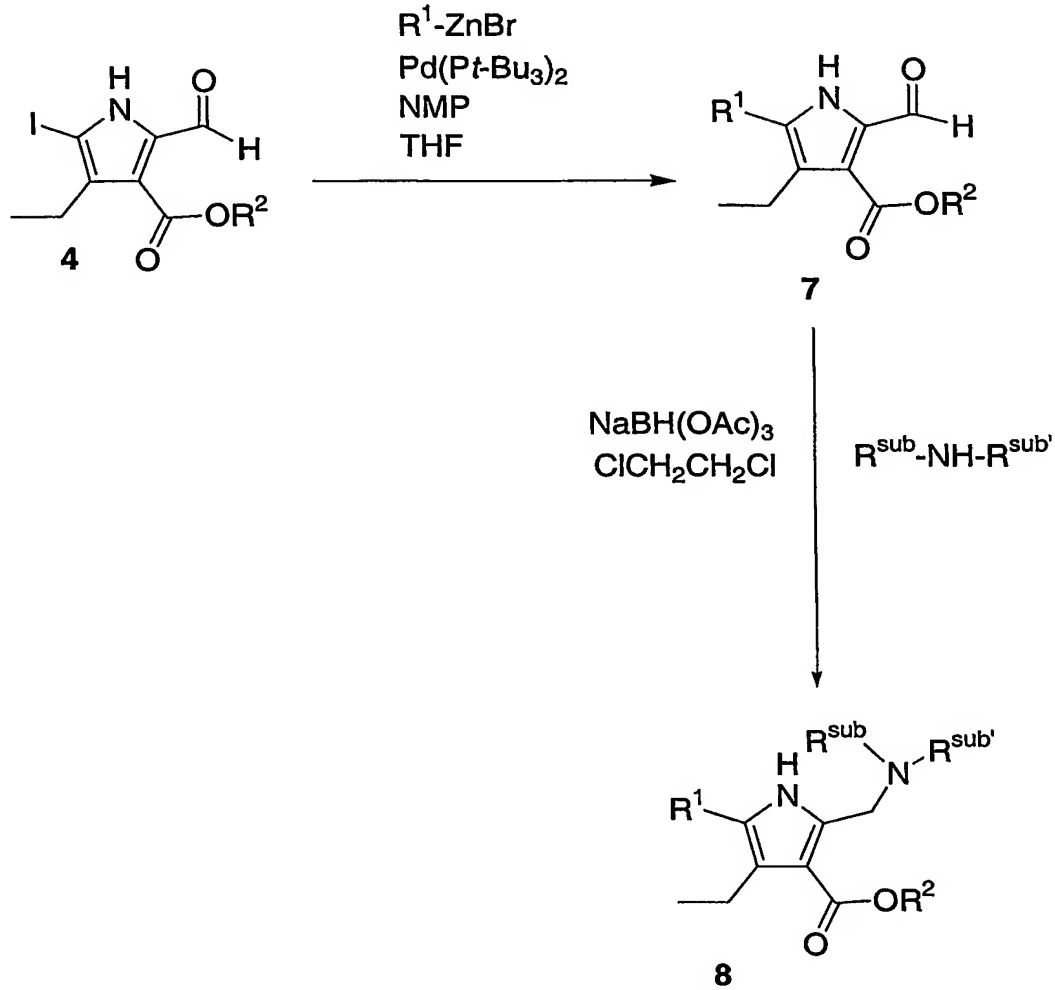
SCHEME 3



SCHEME 4



SCHEME 5

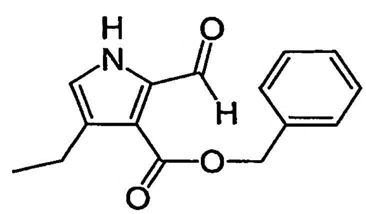

R1-ZnBr
Pd(Pt-Bu3)2
NMP
THF
4
7
NaBH(OAc)3
ClCH2CH2Cl
Rsub-NH-Rsub'
8

EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limiting of the reasonable scope thereof.

EXAMPLE 1

benzyl 4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



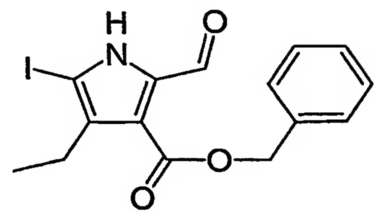
Step A: To a solution of 4-benzyl 2-tert-butyl 3-ethyl-5-methyl-1H-pyrrole-2,4-dicarboxylate (PCT Publ. WO 03/035616) (99.9 mg, 0.291 mmol) in CH_2Cl_2 (0.6 mL, 9.31 mmol) was added triethylsilane (0.12 mL, 0.73 mmol) followed by trifluoroacetic acid (0.29 mL, 3.78 mmol). After the reaction had been stirred at ambient temperature for 3h, it was cooled to 0°C prior to the addition of ice cold 1N $NaHCO_3$ (0.29 mL). The mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. The resultant residue was purified by normal phase chromatography to afford the decarboxylated product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (broad s, 1 H); 7.28-7.42 (m, 5 H); 6.34 (broad s, 1 H); 5.28 (s, 2 H); 2.71 (q, J = 7.5 Hz, 2 H); 2.47 (s, 3 H); 1.15 (t, J = 7.3 Hz, 3 H).

Step B: To a stirred solution of benzyl 4-ethyl-2-methyl-1*H*-pyrrole-3-carboxylate (7.01 mg, 0.29 mmol) in THF (3.4 mL), acetic acid (4.2 mL) and water (3.4 mL) at ambient temperature was added ceric ammonium nitrate (0.6316 g, 1.15 mmol). After 5h, the reaction was poured into water (100mL) and extracted with CH_2Cl_2 (3x 50 mL). The combined organic layers were washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. The resultant residue was purified by normal phase chromatography. Proton NMR for the product was consistent with the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.13 (s, 1 H); 7.35-7.44 (m, 5 H); 6.85 (broad s, 1 H); 5.36 (s, 2 H); 2.78 (q, J = 7.6 Hz, 2

H); 1.20 (t, J = 7.6 Hz, 3 H). HRMS (ES) mass calculated for $C_{15}H_{16}NO_3$ (M+H): 258.1052. Found by LC/MS 258.1.

EXAMPLE 2

benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate

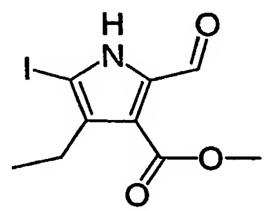


Step A: To a solution of 4-benzyl 2-tert-butyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate (PCT Publ. WO 03/035616) (17.2 mg (0.048 mmol) in CH_2Cl_2 (0.2 mL) was added trifluoroacetic acid (0.1 mL), After the reaction was stirred at ambient temperature for 1h, it was cooled to 0°C prior to the addition of ice cold 1N $NaHCO_3$ (0.1 mL). The mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. The product was not purified.

Step B: To a solution of 4-[(benzyloxy)carbonyl]-3-ethyl-5-formyl-1*H*-pyrrole-2-carboxylic acid (2.85 g, 9.46 mmol) in CH_2Cl_2 (60 mL) was added a solution of $NaHCO_3$ (3.17 g, 37.84 mmol) in water (60 mL). The mixture was stirred vigorously during the addition of a solution of KI (4.71 g, 28.38 mmol) and I_2 (2.59 g, 10.22 mmol) in water (51.6 mL). The resultant mixture was heated to 45°C for 25 min until the initial red/brown color faded. The reaction was cooled to ambient temperature prior to separation of the phases. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The resultant residue was purified by normal phase chromatography (10-25% ethyl acetate/hexanes). Proton NMR for the product was consistent with the title compound. ^1H NMR (500 MHz, $CDCl_3$) δ 9.94 (s, 1 H); 7.35-7.43 (m, 5 H); 5.36 (s, 2 H); 2.69 (q, J = 7.5 Hz, 2 H); 1.08 (t, J = 7.5 Hz, 3 H). HRMS (ES) exact mass calculated for $C_{15}H_{15}INO_3$ (M+H): 384.001. Found 384.3000.

EXAMPLE 3

methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate



Step A: To a solution of 2-tert-butyl 4-methyl 3-ethyl-5-formyl-1H-pyrrole-2,4-dicarboxylate

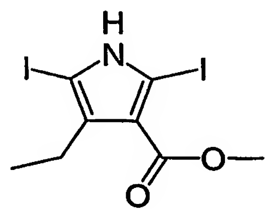
(PCT Publ. WO 03/035615) (85.0 mg, 0.302 mmol) in CH_2Cl_2 (0.62 mL, 9.66 mmol) was added trifluoroacetic acid (0.30 mL, 3.93 mmol). After the reaction was stirred at ambient temperature for 2 h, the reaction was cooled to 0° C prior to the addition of ice cold water. The mixture was extracted by CH_2Cl_2 (3 x 5 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated. Proton NMR of the unpurified material was consistent with the desired product. ^1H NMR (500 MHz, $CDCl_3$) δ 10.27 (s, 1 H); 3.95 (s, 3 H); 3.15 (q, J = 7.3 Hz, 2 H); 1.21 (t, J = 7.3 Hz, 3 H).

Step B: To a solution of 4-[(methoxy)carbonyl]-3-ethyl-5-formyl-1*H*-pyrrole-2-carboxylic acid

(3.80 g, 16.87 mmol) in CH_2Cl_2 (170 mL) was added a solution of $NaHCO_3$ (5.67 g, 67.50 mmol) in water (85 mL). The mixture was stirred vigorously during the addition of a solution of KI (8.40 g, 50.62 mmol) and I_2 (4.63 g, 18.22 mmol) in water (85 mL). The resultant mixture was heated to 45°C for 2 h until the initial red/brown color faded. The reaction was cooled to ambient temperature prior to separation of the phases. The organic layer was washed once with water, dried over Na_2SO_4, filtered, and concentrated. The resultant residue was purified by normal phase chromatography (10-30% ethyl acetate/hexanes). Proton NMR for the product was consistent with the title compound. ^1H NMR (500 MHz, $CDCl_3$) δ 9.95 (s, 1 H); 3.92 (s, 3 H); 2.70 (q, J = 7.5 Hz, 2 H); 1.11 (t, J = 7.5 Hz, 3 H). HRMS (ES) exact mass calculated for $C_9H_{11}INO_3$ (M+H): 307.9778. Found 307.9775

EXAMPLE 4

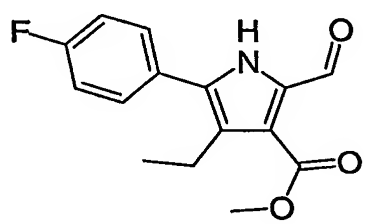
methyl 4-ethyl-2,5-diiodo-1H-pyrrole-3-carboxylate



Following the procedure described in Example 3, the title compound was obtained as a second product. Proton NMR for this product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_9H_{10}I_2NO_2$ (M+H): 427.8615. Found by LC/MS 427.8.

EXAMPLE 5

methyl 5-(4-fluorophenyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate

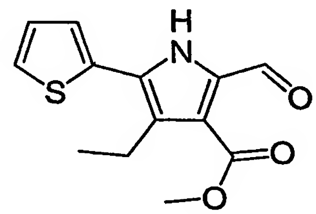


Methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate was obtained following the procedures described in Example 3. To a solution of methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate (0.123 g, 0.40 mmol) in dimethoxyethane (4.0 mL) was added K_3PO_4 (0.426 g, 2.00 mmol), $Pd(PPh_3)_4$ (0.0463 g, 0.04 mmol), and 4-fluorophenylboronic acid (0.0842 g, 0.60 mmol). The reaction was deoxygenated by bubbling argon through the solution prior to being heated to 85°C and refluxed for 16 h under argon. After cooling to ambient temperature, the reaction was filtrated through a pad of silica gel and concentration. The resultant residue was dissolved in acetonitrile and purified by reverse phase HPLC. Proton NMR for the product was consistent with the title compound. ^1H NMR (500 MHz, $CDCl_3$) δ 10.15 (s, 1 H); 7.43 (dd, J = 3.4, 5.2 Hz, 2 H); 7.18 (app t, 8.6 Hz, 2 H);

3.94 (s, 3 H); 2.80 (q, J = 7.4 Hz, 2 H); 1.22 (t, J = 7.4 Hz, 3 H). HRMS (ES) exact mass calculated $C_{15}H_{15}FNO_3$ (M+H): 276.1312. Found 276.1264

EXAMPLE 6

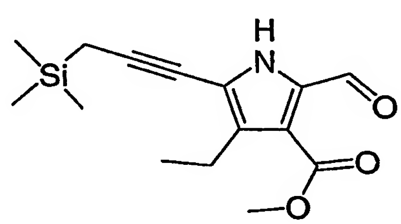
methyl 4-ethyl-2-formyl-5-thien-2-yl-1H-pyrrole-3-carboxylate



Methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate was obtained following the procedures described in Example 3. To a solution of methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate (0.123 g, 0.40 mmol) and bromo(thien-2-yl)zinc (0.1374 g, 0.60 mmol) in THF (2.0 mL) was added Pd(P*t*-Bu_3)$_2$ (0.0123 g, 0.02 mmol) and *N*-methylpyrrolidine (2.0 mL). The reaction was deoxygenated by bubbling argon through the solution prior to being heated to 100°C and refluxed for 4h under argon. After cooling to ambient temperature, the reaction was filtered through a pad of silica gel and concentrated. The resultant residue was dissolved in acetonitrile and purified by reverse phase HPLC. Proton NMR for the product was consistent with the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.14 (s, 1 H); 7.42 (d, J = 5.1 Hz, 1 H); 7.24 (d, J = 3.7 Hz, 1 H); 7.14 (dd, J = 3.7, 4.7 Hz, 1 H); 3.94 (s, 3 H); 2.94 (q, J = 7.4 Hz, 2 H); 1.24 (t, J = 7.4 Hz, 3 H). HRMS (ES) exact mass calculated $C_{13}H_{14}NO_3S$ (M+H): 264.0689. Found 264.0688

EXAMPLE 7

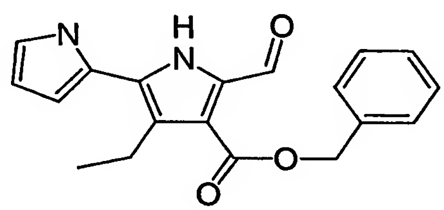
methyl 4-ethyl-2-formyl-5-[3-(trimethylsilyl)prop-1-ynyl]-1H-pyrrole-3-carboxylate



Methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate was obtained following the procedures described in Example 3. $Pd(Pt\text{-}Bu_3)_4$ (18.4 mg, 0.040 mmol), $Pd_2(dba)_3$ (16.5 mg, 0.020 mmol), and CuI (4.6 mg, 0.020 mmol) were combined in a dry flask under N_2 prior to evacuating the flask and refilling with argon. After the flask was charged with dioxane (4.0 mL), i-Pr_2NEt (0.0675 mL, 0.48 mmol), trimethyl(prop-2-ynyl)silane (90.0 mg, 0.80 mmol), and methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate (123.0 mg, 0.40 mmol) were added sequentially. The reaction was stirred overnight at 80°C. After the reaction was cooled to ambient temperature, it was filtered through a plug of silica gel and concentrated *in vacuo*. The resultant residue was dissolved in acetonitrile and purified by reverse phase HPLC. Proton NMR for the product was consistent with the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.04 (s, 1 H); 3.90 (s, 3 H); 2.78 (q, J = 7.5 Hz, 2 H); 1.77 (s, 2 H); 1.16 (t, J = 7.5 Hz, 3 H); 0.17 (s, 9 H). HRMS (ES) exact mass calculated $C_{15}H_{22}NO_3Si$ (M+H): 292.1364. Found 292.1364

EXAMPLE 8

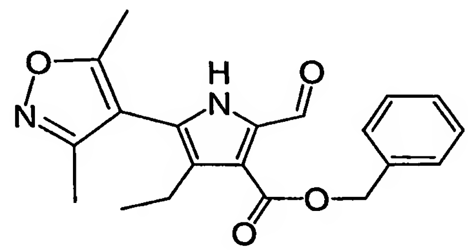
4'-benzyl 1-tert-butyl 3'-ethyl-5'-formyl-1H,1'H-2,2'-bipyrrole-1,4'-dicarboxylate



Following the procedures described in Example 5, replacing methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate with benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate and 4-fluorophenylboronic acid with 1-(tert-butoxycarbonyl)-1H-pyrrol-2-ylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{19}H_{19}N_2O_3$ (M+H): 323.1390. Found 323.1384.

EXAMPLE 9

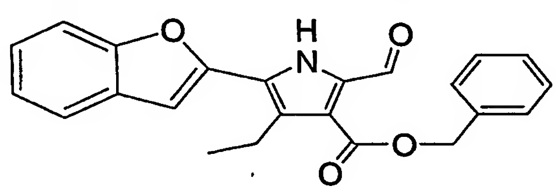
benzyl 5-(3,5-dimethylisoxazol-4-yl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate with benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate and 4-fluorophenylboronic acid with 3,5-dimethylisoxazol-4-ylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{21}N_2O_4$ (M+H): 353.1502. Found 353.1496

EXAMPLE 10

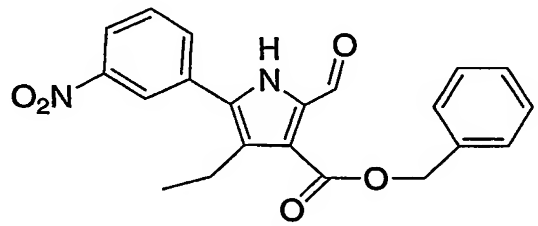
benzyl 5-(1-benzofuran-2-yl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate with benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate and 4-fluorophenylboronic acid with 1-benzofuran-2-ylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{23}H_{20}NO_4$ (M+H): 374.1372. Found 374.1387

EXAMPLE 11

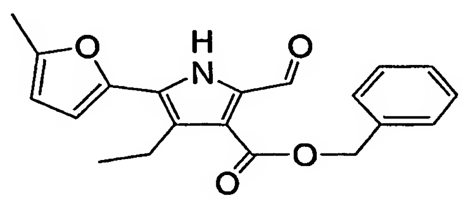
benzyl 4-ethyl-2-formyl-5-(3-nitrophenyl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate with benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate and 4-fluorophenylboronic acid with 3-nitrophenylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{19}N_2O_5$ (M+H): 379.1289. Found 379.1290

EXAMPLE 12

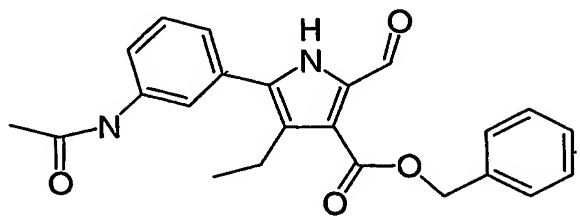
benzyl 4-ethyl-2-formyl-5-(5-methyl-2-furyl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate with benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate and 4-fluorophenylboronic acid with 5-methyl-2-furylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{20}NO_4$ (M+H): 338.1382. Found 338.1387

EXAMPLE 13

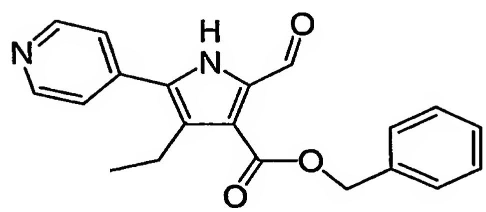
benzyl 5-[3-(acetylamino)phenyl]-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate with benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate and 4-fluorophenylboronic acid with 3-(acetylamino) phenylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{23}H_{23}N_2O_4$ (M+H): 391.1653. Found 391.1651

EXAMPLE 14

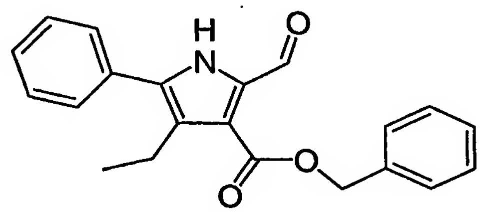
benzyl 4-ethyl-2-formyl-5-pyridin-4-yl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate with benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate and 4-fluorophenylboronic acid with pyridin-4-ylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{19}N_2O_3$ (M+H): 335.1390. Found 335.1402

EXAMPLE 15

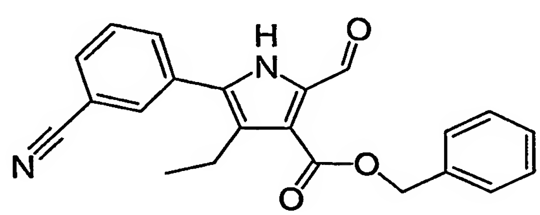
benzyl 4-ethyl-2-formyl-5-phenyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate with benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate and 4-fluorophenylboronic acid with phenylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. . ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.39 (broad s, 1 H); 7.36-7.50 (m, 5 H); 5.40 (s, 2 H); 2.85 (q, J = 7.3 Hz, 2 H); 1.22 (t, J = 7.3 Hz, 3 H). HRMS (ES) exact mass calculated for $C_{21}H_{20}NO_3$ (M+H): 334.1938. Found 334.1430

EXAMPLE 16

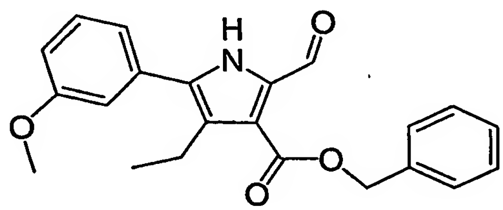
benzyl 5-(3-cyanophenyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate with benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate and 4-fluorophenylboronic acid with 3-cyanophenylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{22}H_{19}N_2O_3$ (M+H): 359.1390. Found 359.1394

EXAMPLE 17

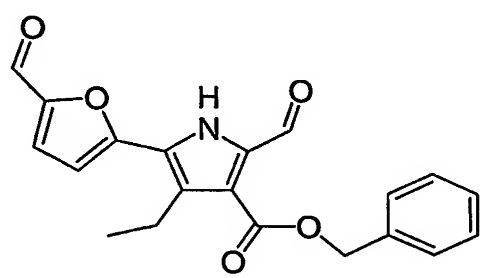
benzyl 4-ethyl-2-formyl-5-(3-methoxyphenyl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate with benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate and 4-fluorophenylboronic acid with 3-methoxyphenylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.14 (s, 1 H); 7.45 (m, 2 H); 7.36-7.41 (m, 4 H); 7.02 (m 2 H); 6.96 (m, 2 H); 5.39 (s, 2 H); 3.85 (s, 3 H); 2.85 (q, J = 7.3 Hz, 2 H); 1.21 (t, J = 7.3 Hz, 3 H). HRMS (ES) exact mass calculated for $C_{22}H_{22}NO_4$ (M+H): 364.1594. Found 364.1573

EXAMPLE 18

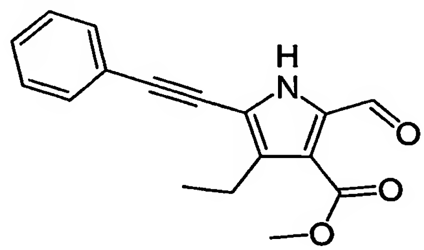
benzyl 4-ethyl-2-formyl-5-(5-formyl-2-furyl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate with benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate and 4-fluorophenylboronic acid with 5-formyl-2-furylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{18}NO_5$ (M+H): 352.1180. Found 352.1183

EXAMPLE 19

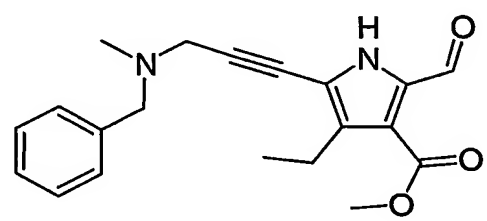
methyl 4-ethyl-2-formyl-5-(phenylethynyl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 7, replacing trimethyl (prop-2-ynyl)silane with ethynylbenzene, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{17}H_{16}NO_3$ (M+H): 282.1125. Found 282.1121

EXAMPLE 20

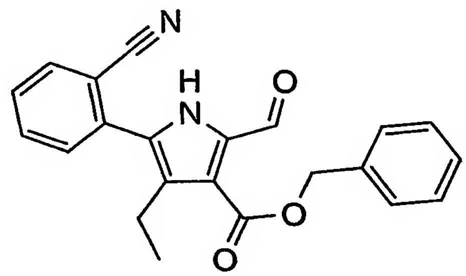
methyl 5-{3-[benzyl(methyl)amino]prop-1-ynyl}-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 7, replacing trimethyl(prop-2-ynyl)silane with N-benzyl-N-methyl-N-prop-2-ynylamine, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{20}H_{23}N_2O_3$ (M+H): 339.1703. Found 339.1703

EXAMPLE 21

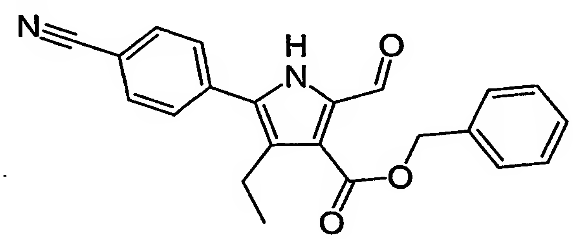
benzyl 5-(2-cyanophenyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate with benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate and 4-fluorophenylboronic acid with 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzonitrile, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{22}H_{19}N_2O_3$ (M+H): 359.1390. Found 359.1386

EXAMPLE 22

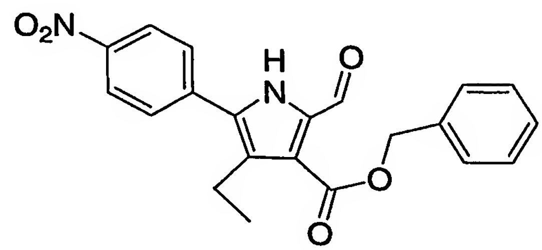
benzyl 5-(4-cyanophenyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing of methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate with benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate and 4-fluorophenylboronic acid with 4-cyanophenylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{22}H_{19}N_2O_3$ (M+H): 359.1390. Found 359.1387

EXAMPLE 23

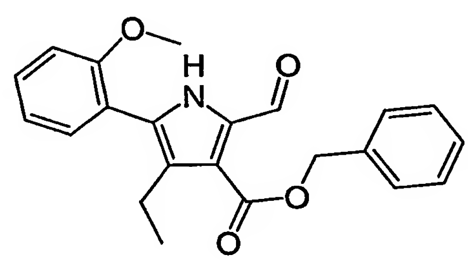
benzyl 4-ethyl-2-formyl-5-(4-nitrophenyl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate with benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate and 4-fluorophenylboronic acid with 4-nitrophenylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{19}N_2O_5$ (M+H): 379.1216. Found 379.1270

EXAMPLE 24

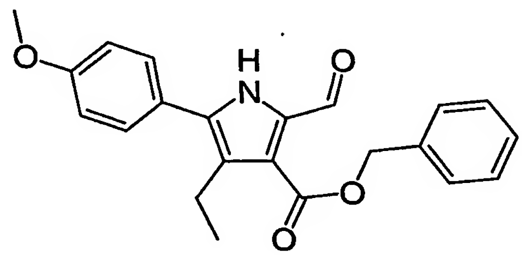
benzyl 4-ethyl-2-formyl-5-(2-methoxyphenyl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate with benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate and 4-fluorophenylboronic acid with 2-methoxyphenylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{22}H_{22}NO_4$ (M+H): 364.1544. Found 364.1537

EXAMPLE 25

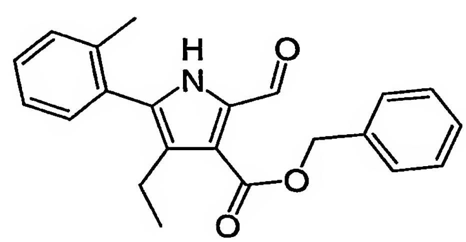
benzyl 4-ethyl-2-formyl-5-(4-methoxyphenyl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate with benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate and 4-fluorophenylboronic acid with 4-methoxyphenylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{22}H_{22}NO_4$ (M+H): 364.1544. Found 364.1536

EXAMPLE 26

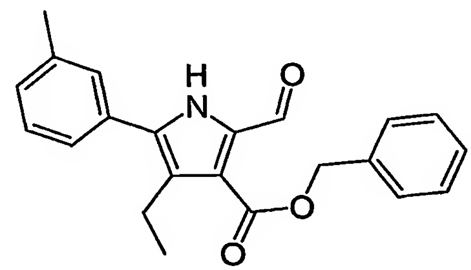
benzyl 4-ethyl-2-formyl-5-(2-methylphenyl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate with benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate and 4-fluorophenylboronic acid with 2-methylphenylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{22}H_{22}NO_3$ (M+H): 348.1594. Found 348.1603

EXAMPLE 27

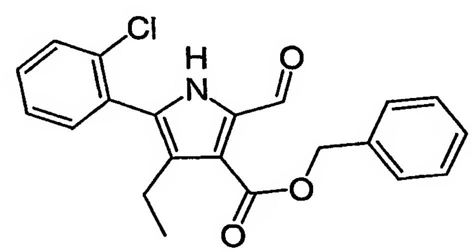
benzyl 4-ethyl-2-formyl-5-(3-methylphenyl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate with benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate and 4-fluorophenylboronic acid with 3-methylphenylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{22}H_{22}NO_3$ (M+H): 348.1594. Found 348.1611

EXAMPLE 28

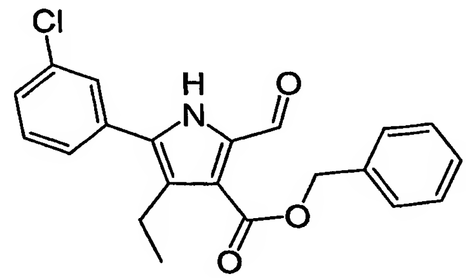
benzyl 5-(2-chlorophenyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate with benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate and 4-fluorophenylboronic acid with 2-chloro phenylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{19}ClNO_3$ (M+H): 368.1048. Found 368.1015

EXAMPLE 29

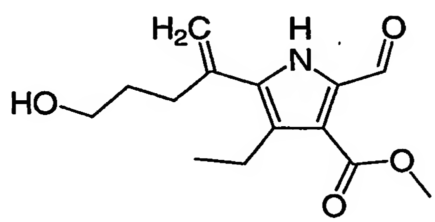
benzyl 5-(3-chlorophenyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing methyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate with benzyl 4-ethyl-2-formyl-5-iodo-1H-pyrrole-3-carboxylate and 4-fluorophenylboronic acid with 3-chloro phenylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated for $C_{21}H_{19}ClNO_3$ (M+H): 368.1048. Found 368.1018

EXAMPLE 30

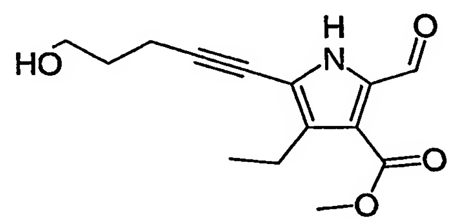
methyl 4-ethyl-2-formyl-5-[1-(3-hydroxypropyl)vinyl]-1H-pyrrole-3-carboxylate



Following the procedures described in Example 7, replacing trimethyl(prop-2-ynyl)silane with pent-4-yn-1-ol, the title compound was obtained as a second product. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{14}H_{20}NO_4$ (M+H): 266.1387. Found 266.1388

EXAMPLE 31

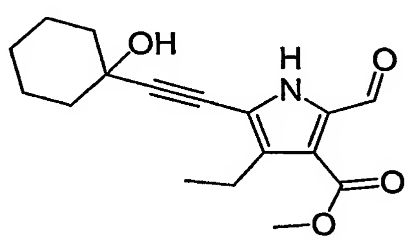
methyl 4-ethyl-2-formyl-5-(5-hydroxypent-1-ynyl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 7, replacing trimethyl(prop-2-ynyl)silane with pent-4-yn-1-ol, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{14}H_{18}NO_4$ (M+H): 264.1231. Found 264.1227

EXAMPLE 32

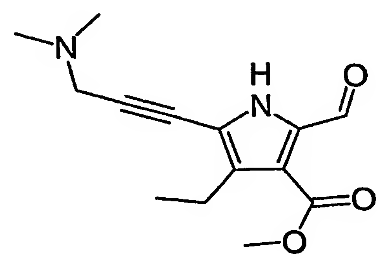
methyl 4-ethyl-2-formyl-5-[(1-hydroxycyclohexyl)ethynyl]-1H-pyrrole-3-carboxylate



Following the procedures described in Example 7, replacing trimethyl(prop-2-ynyl)silane with 1-ethynylcyclohexanol, the title compound was obtained. Proton NMR for the product was consistent with the title compound. . ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.09 (s, 1 H); 3.91 (s, 3 H); 2.81 (q, J = 7.5 Hz, 2 H); 1.52-2.03 (m, 10 H); 1.17 (t, J = 7.5 Hz, 3 H). HRMS (ES) exact mass calculated $C_{17}H_{22}NO_4$ (M+H): 304.1544. Found 304.1536

EXAMPLE 33

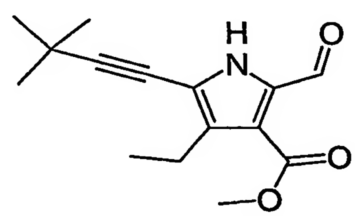
methyl 5-[3-(dimethylamino)prop-1-ynyl]-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 7, replacing trimethyl(prop-2-ynyl)silane with N,N-dimethyl-N-prop-2-ynylamine, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{14}H_{19}N_2O_3$ (M+H): 263.1390. Found 263.1388

EXAMPLE 34

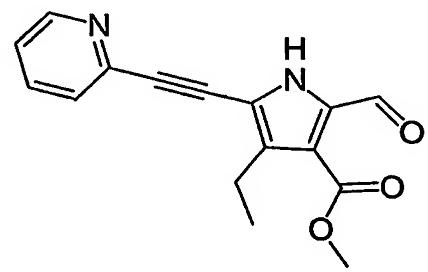
methyl 5-(3,3-dimethylbut-1-ynyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 7, replacing trimethyl(prop-2-ynyl)silane with 3,3-dimethylbut-1-yne, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{15}H_{20}NO_3$ (M+H): 262.1438. Found 262.1440

EXAMPLE 35

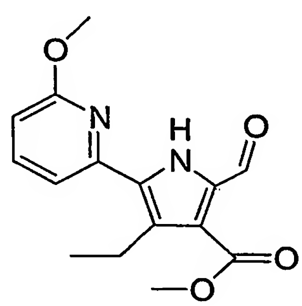
methyl 4-ethyl-2-formyl-5-(pyridin-2-ylethynyl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 7, replacing trimethyl(prop-2-ynyl)silane with 2-ethynylpyridine, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{16}H_{15}N_2O_3$ (M+H): 283.1077. Found 283.1065

EXAMPLE 36

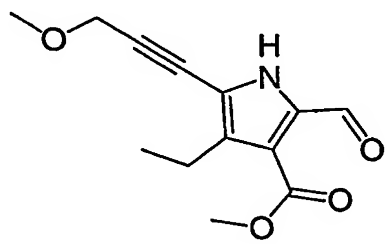
methyl 4-ethyl-2-formyl-5-(6-methoxypyridin-2-yl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing 4-fluorophenylboronic acid with bromo(6-methoxypyridin-2-yl)zinc, the title compound was obtained. Proton NMR for the product was consistent with the title compound as a 3:1 ratio of atropdiastereomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.22 (s, 0.25 H); 10.19 (s, 0.75 H); 7.66 (app. t, J = 7.6 Hz, 1 H); 7.25 (m, 1 H), 6.72 (app. d, J = 8.3 Hz, 1 H); 4.02 (s, 3 H); 3.94 (s, 2.25 H); 3.93 (s, 0.75 H); 2.69 (m, 2 H); 1.31 (t, J = 7.4 Hz, 2.25 H); 1.18 (t, J = 7.4 Hz, 0.75 H). HRMS (ES) exact mass calculated $C_{15}H_{17}N_2O_4$ (M+H): 289.1183. Found 289.1184

EXAMPLE 37

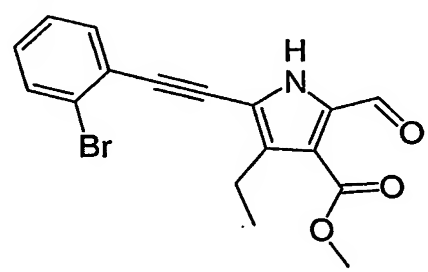
methyl 4-ethyl-2-formyl-5-(3-methoxyprop-1-ynyl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 7, replacing trimethyl(prop-2-ynyl)silane with 3-methoxyprop-1-yne, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{13}H_{16}NO_4$ (M+H): 250.1231. Found 250.1231

EXAMPLE 38

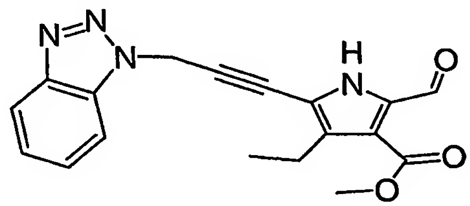
methyl 5-[(2-bromophenyl)ethynyl]-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 7, replacing trimethyl(prop-2-ynyl)silane with 1-bromo-2-ethynylbenzene, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{17}H_{15}BrNO_3$ (M+H): 360.0230. Found 360.0232

EXAMPLE 39

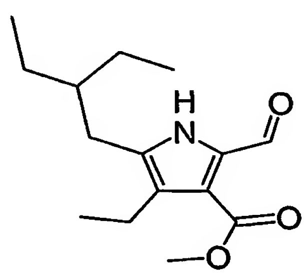
methyl 5-[3-(1H-1,2,3-benzotriazol-1-yl)prop-1-ynyl]-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 7, replacing trimethyl(prop-2-ynyl)silane with 1-prop-2-ynyl-1H-1,2,3-benzotriazole, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{18}H_{17}N_4O_3$ (M+H): 337.1295. Found 337.1297

EXAMPLE 40

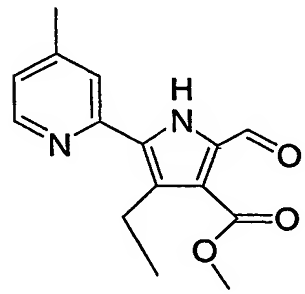
methyl 4-ethyl-5-(2-ethylbutyl)-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 6, replacing bromo(thien-2-yl)zinc with bromo(2-ethylbutyl)zinc, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{15}H_{24}NO_3$ (M+H): 266.1751. Found 266.1749

EXAMPLE 41

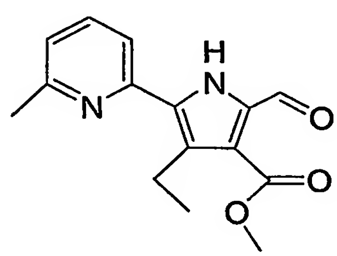
methyl 4-ethyl-2-formyl-5-(4-methylpyridin-2-yl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 6, replacing bromo(thien-2-yl)zinc with bromo(4-methylpyridin-2-yl)zinc, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{15}H_{17}N_2O_3$ (M+H): 273.1234. Found 273.1224

EXAMPLE 42

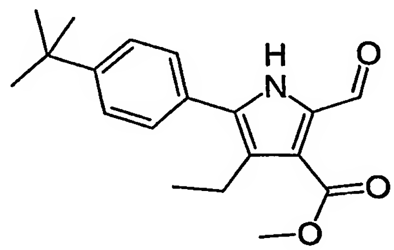
methyl 4-ethyl-2-formyl-5-(6-methylpyridin-2-yl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 6, replacing bromo(thien-2-yl)zinc with bromo(6-methylpyridin-2-yl)zinc, the title compound was obtained. Proton NMR for the product was consistent with the title compound. . ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.24 (s, 1 H); 8.04 (t, J = 7.8 Hz, 1 H); 7.67 (d, J = 8.0 Hz , 1 H); 7.37 (d, J = 7.7 Hz, 1 H); 3.95 (s, 3 H); 3.01 (q, J = 7.4 Hz, 2 H); 2.75 (s, 3 H); 1.31 (t, J = 7.4 Hz, 3 H). HRMS (ES) exact mass calculated $C_{15}H_{17}N_2O_3$ (M+H): 273.1234. Found 273.1227

EXAMPLE 43

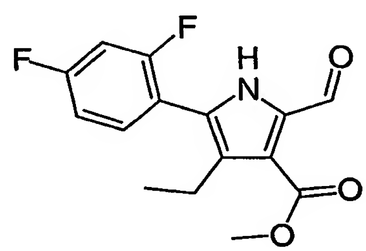
methyl 5-(4-tert-butylphenyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing and 4-fluorophenylboronic acid with 4-*tert*-butylphenylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{19}H_{24}NO_3$ (M+H): 314.1751. Found 314.1743

EXAMPLE 44

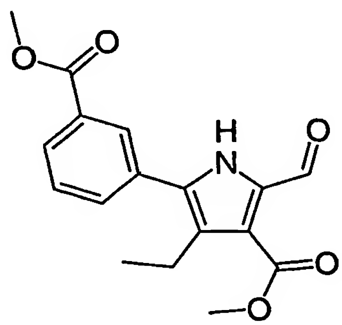
methyl 5-(2,4-difluorophenyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing and 4-fluorophenylboronic acid with 2,4-difluorophenyl boronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{15}H_{14}F_2NO_3$ (M+H): 294.0863. Found 294.0937

EXAMPLE 45

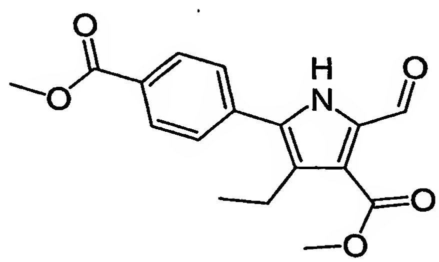
methyl 4-ethyl-2-formyl-5-[3-(methoxycarbonyl)phenyl]-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing and 4-fluorophenylboronic acid with 3-(methoxycarbonyl)phenyl boronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{17}H_{18}NO_5$ (M+H): 316.1180. Found 316.1173

EXAMPLE 46

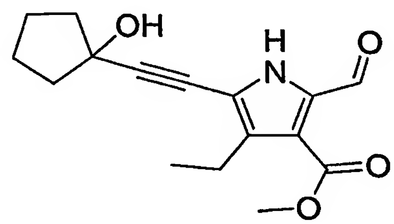
methyl 4-ethyl-2-formyl-5-[4-(methoxycarbonyl)phenyl]-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing and 4-fluorophenylboronic acid with 4-(methoxycarbonyl) phenyl boronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{17}H_{18}NO_5$ (M+H): 316.1180. Found 316.1181

EXAMPLE 47

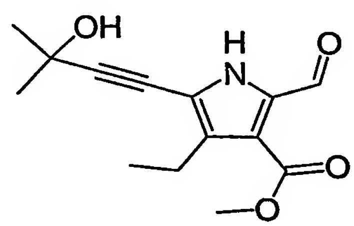
methyl 4-ethyl-2-formyl-5-[(1-hydroxycyclopentyl)ethynyl]-1H-pyrrole-3-carboxylate



Following the procedures described in Example 7, replacing trimethyl(prop-2-ynyl)silane with 1-ethynylcyclopentanol, the title compound was obtained. Proton NMR for the product was consistent with the title compound. . ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.09 (s, 1 H); 3.91 (s, 3 H); 2.80 (q, J = 7.5 Hz, 2 H); 1.78-2.07 (m, 8 H); 1.17 (t, J = 7.5 Hz, 3 H). HRMS (ES) exact mass calculated $C_{16}H_{20}NO_4$ (M+H): 290.1387. Found 290.1408

EXAMPLE 48

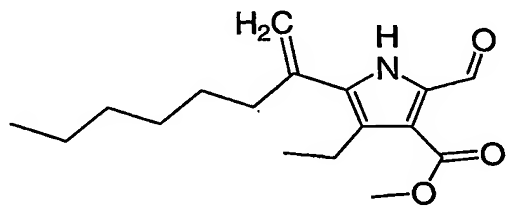
methyl 4-ethyl-2-formyl-5-(3-hydroxy-3-methylbut-1-ynyl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 7, replacing trimethyl(prop-2-ynyl)silane with 2-methylbut-3-yn-2-ol, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{14}H_{18}NO_4$ (M+H): 264.1231. Found 264.1234

EXAMPLE 49

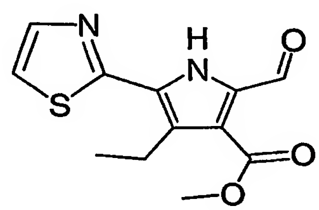
methyl 4-ethyl-2-formyl-5-(1-hexylvinyl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 7, replacing trimethyl(prop-2-ynyl)silane with oct-1-yne, the title compound was obtained as the major product. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{17}H_{26}NO_3$ (M+H): 292.1907. Found 292.1897

EXAMPLE 50

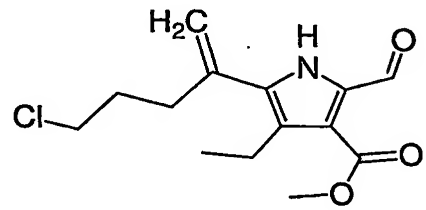
methyl 4-ethyl-2-formyl-5-(1,3-thiazol-2-yl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 6, replacing bromo(thien-2-yl)zinc with bromo(1,3-thiazol-2-yl)zinc, the title compound was obtained. Proton NMR for the product was consistent with the title compound. . ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.23 (s, 1 H); 7.88 (d, J = 3.2 Hz, 1 H); 7.43 (d, J = 3.1 Hz, 1 H); 3.95 (s, 3 H); 3.12 (q, J = 7.5 Hz, 2 H); 1.28 (t, J = 7.5 Hz, 3 H). HRMS (ES) exact mass calculated $C_{12}H_{13}N_2O_3S$ (M+H): 265.0642. Found 265.0644

EXAMPLE 51

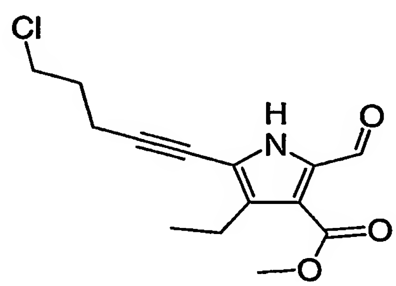
methyl 5-[1-(3-chloropropyl)vinyl]-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 7, replacing trimethyl(prop-2-ynyl)silane with 5-chloropent-1-yne, the title compound was obtained as a second product. Proton NMR for the product was consistent with the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.10 (s, 1 H); 5.39 (s, 1 H); 5.32 (s, 1 H); 3.92 (s, 3 H); 3.54 (t, J = 6.4 Hz, 2 H); 2.79 (q, J = 7.3 Hz, 2 H); 2.59 (t, J = 7.3 Hz, 2 H); 1.87 (m, 2 H); 1.17 (t, J = 7.3 Hz, 3 H). HRMS (ES) exact mass calculated $C_{14}H_{19}ClNO_3$ (M+H): 284.1048. Found 284.1069

EXAMPLE 52

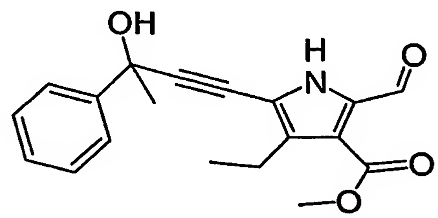
methyl 5-(5-chloropent-1-ynyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 7, replacing trimethyl(prop-2-ynyl)silane with 5-chloropent-1-yne, the title compound was obtained. Proton NMR for the product was consistent with the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.07 (s, 1 H); 3.91 (s, 3 H); 3.70 (t, J = 6.4 Hz, 2 H); 2.79 (q, J = 7.6 Hz, 2 H); 2.68 (t, J = 6.4 Hz, 2 H); 2.08 (quint, J = 6.6 Hz, 2 H); 1.16 (t, J = 7.6 Hz, 3 H). HRMS (ES) exact mass calculated $C_{14}H_{17}ClNO_3$ (M+H): 282.0892. Found 282.0889

EXAMPLE 53

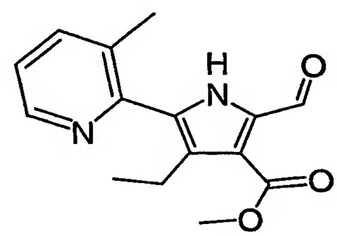
methyl 4-ethyl-2-formyl-5-(3-hydroxy-3-phenylbut-1-ynyl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 7, replacing trimethyl(prop-2-ynyl)silane with 2-phenylbut-3-yn-2-ol, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{19}H_{20}NO_4$ (M+H): 326.1387. Found 326.1386

EXAMPLE 54

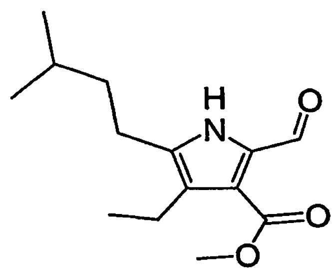
methyl 4-ethyl-2-formyl-5-(3-methylpyridin-2-yl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 6, replacing bromo(thien-2-yl)zinc with bromo(3-methylpyridin-2-yl)zinc, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{15}H_{17}N_2O_3$ (M+H): 273.1234. Found 273.1235

EXAMPLE 55

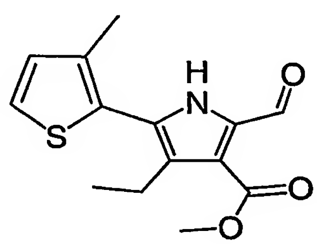
methyl 4-ethyl-2-formyl-5-isopentyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 6, replacing bromo(thien-2-yl)zinc of step Z with bromo(isopentyl)zinc, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{14}H_{22}NO_3$ (M+H): 252.1594. Found 252.1593

EXAMPLE 56

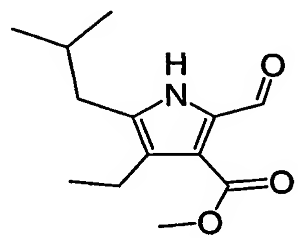
methyl 4-ethyl-2-formyl-5-(3-methylthien-2-yl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 6, replacing bromo(thien-2-yl)zinc with bromo(3-methylthien-2-yl)zinc, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{14}H_{16}NO_3S$ (M+H): 278.0846. Found 278.0864

EXAMPLE 57

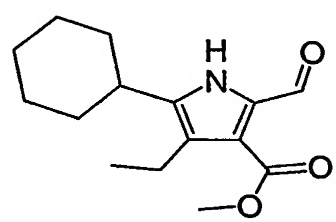
methyl 4-ethyl-2-formyl-5-isobutyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 6, replacing bromo(thien-2-yl)zinc with bromo(isobutyl)zinc, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{13}H_{20}NO_3$ (M+H): 238.1438. Found 238.1435

EXAMPLE 58

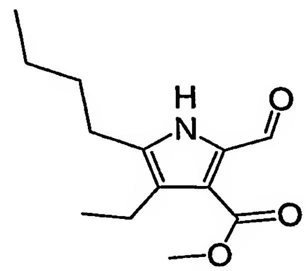
methyl 5-cyclohexyl-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 6, replacing bromo(thien-2-yl)zinc with bromo(cyclohexyl)zinc, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{15}H_{22}NO_3$ (M+H): 264.1594. Found 264.1608

EXAMPLE 59

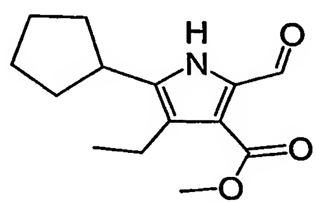
methyl 5-butyl-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 6, replacing bromo(thien-2-yl)zinc with bromo(butyl)zinc, the title compound was obtained. Proton NMR for the product was consistent with the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.03 (s, 1 H); 3.90 (s, 3 H); 2.69 (q, J = 7.4 Hz, 2 H); 2.61 (t, J = 7.7 Hz, 2 H); 1.61 (m, 2 H); 1.37 (m, 2 H); 1.13 (t, J = 7.4 Hz, 3 H); 0.94 (t, J = 7.4 Hz, 3 H). HRMS (ES) exact mass calculated $C_{13}H_{20}NO_3$ (M+H): 238.1438. Found 238.1435

EXAMPLE 60

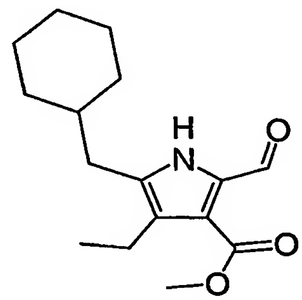
methyl 5-cyclopentyl-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 6, replacing bromo(thien-2-yl)zinc with bromo(cyclopentyl)zinc, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{14}H_{20}NO_3$ (M+H): 250.1438. Found 250.1459

EXAMPLE 61

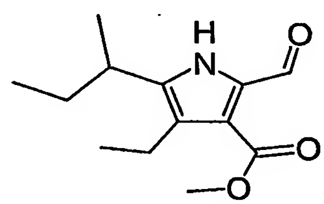
methyl 5-(cyclohexylmethyl)-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 6, replacing bromo(thien-2-yl)zinc with bromo-(cyclohexylmethyl)zinc, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{16}H_{24}NO_3$ (M+H): 278.1751. Found 278.1757

EXAMPLE 62

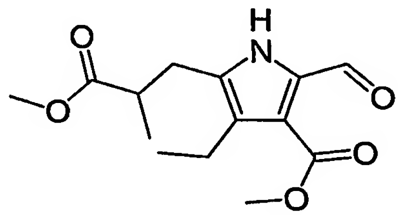
methyl 5-sec-butyl-4-ethyl-2-formyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 6, replacing bromo(thien-2-yl)zinc with bromo(sec-butyl)zinc, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{13}H_{20}NO_3$ (M+H): 238.1438. Found 238.1425

EXAMPLE 63

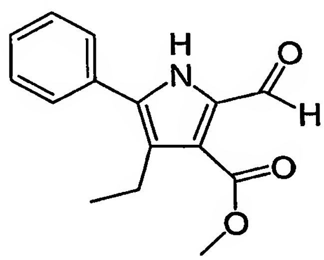
methyl 4-ethyl-2-formyl-5-(3-methoxy-2-methyl-3-oxopropyl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 6, replacing bromo(thien-2-yl)zinc with bromo(3-methoxy-2-methyl-3-oxopropyl)zinc, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{14}H_{20}NO_5$ (M+H): 282.1336. Found 282.1345

EXAMPLE 64

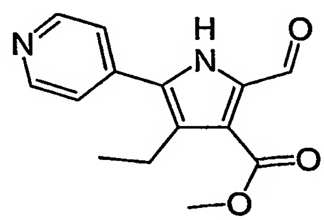
methyl 4-ethyl-2-formyl-5-phenyl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing 4-fluorophenylboronic acid with phenylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{15}H_{16}NO_3$ (M+H): 258.1052. Found 258.3200

EXAMPLE 65

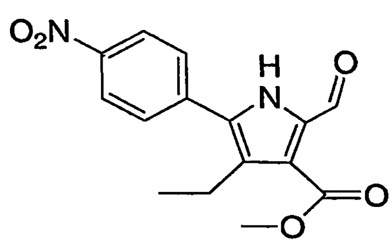
methyl 4-ethyl-2-formyl-5-pyridin-4-yl-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing 4-fluorophenylboronic acid with pyridin-4-ylboronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{14}H_{15}N_2O_3$ (M+H): 259.1077. Found 259.1081

EXAMPLE 66

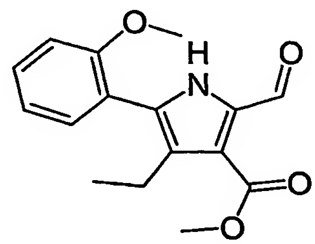
methyl 4-ethyl-2-formyl-5-(4-nitrophenyl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing 4-fluorophenylboronic acid with 4-nitrophenyl boronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{15}H_{15}N_2O_5$ (M+H): 303.0976. Found 303.0979

EXAMPLE 67

methyl 4-ethyl-2-formyl-5-(2-methoxyphenyl)-1H-pyrrole-3-carboxylate



Following the procedures described in Example 5, replacing 4-fluorophenylboronic acid with 2-methoxyphenyl boronic acid, the title compound was obtained. Proton NMR for the product was consistent with the title compound. HRMS (ES) exact mass calculated $C_{16}H_{18}NO_4$ (M+H): 288.1158. Found by LC/MS 288.35.

ASSAYS

The compounds of the instant invention described in the Examples above were tested by the assays described below and were found to have kinase inhibitory activity. In particular, the compounds of the instant invention inhibited IGF-1R or insulin receptor kinase activity with an IC_{50} of less than or equal to about 100 μM. Other assays are known in the literature and could be readily performed by those with skill in the art (see for example, Dhanabal *et al.*, *Cancer Res.* 59:189-197; Xin *et al.*, *J. Biol. Chem.* 274:9116-9121; Sheu *et al.*, *Anticancer Res.* 18:4435-4441; Ausprunk *et al.*, *Dev. Biol.* 38:237-248; Gimbrone *et al.*, *J. Natl. Cancer Inst.* 52:413-427; Nicosia *et al.*, *In Vitro* 18:538-549).

IGF-1R KINASE ASSAY

IGF-1R receptor kinase activity is measured by incorporation of phosphate into a peptide substrate containing a tyrosine residue. Phosphorylation of the peptide substrate is quantitated using anti-IGF-1R and anti-phosphotyrosine antibodies in an HTRF (Homogeneous Time Resolved Fluorescence) detection system. (Park, Y-W., et al. Anal. Biochem., (1999) 269, 94-104)

MATERIALS

IGF-1R RECEPTOR KINASE DOMAIN

The intracellular kinase domain of human IGF-1R was cloned as a glutathione S-transferase fusion protein. IGF-1R β-subunit amino acid residues 930 to 1337 (numbering system as per Ullrich et al., EMBO J. (1986) 5, 2503-2512) were cloned into the baculovirus transfer vector pAcGHLT-A (BD-Pharmingen) such that the N-terminus of the IGF-1R residues are fused to the C-terminus of the GST domain encoded in the transfer vector pAcGHLT-A. Recombinant virus was generated and the fusion protein expressed in SF-9 insect cells (BD-Pharmingen). Enzyme was purified by means of a glutathione sepharose column.

INSULIN RECEPTOR KINASE DOMAIN

The intracellular kinase domain of human insulin receptor was cloned as a glutathione S-transferase fusion protein. Insulin receptor β-subunit amino acid residues 941 to1343 (numbering system as per Ullrich et al., Nature, (1985) 313, 756-761) were cloned into the baculovirus transfer vector pAcGHLT-A (BD-Pharmingen) such that the N-terminus of the IGF-1R residues are fused to the C-terminus of the GST domain encoded in the transfer vector pAcGHLT-A. Recombinant virus was generated and the fusion protein expressed in SF-9 insect cells (BD-Pharmingen) Enzyme was purified by means of a glutathione sepharose column.

INSECT CELL LYSIS BUFFER

10mM Tris pH 7.5; 130mM NaCl; 2mM DTT; 1% Triton X-100; 10mM NaF; 10mM NaPi; 10mM NaPPi; 1X protease inhibitor cocktail (Pharmingen).

WASH BUFFER

Phosphate Buffered Saline (PBS): 137Mm NaCl, 2.6mM KCl, 10mM Na_2HPO_4, 1.8mM KH_2PO_4, pH 7.4; 1mM DTT; 1X protease inhibitor cocktail

DIALYSIS BUFFER

20mM Tris pH 7.5; 1mM DTT; 200mM NaCl; 0.05% Triton X-100 and 50% glycerol

ENZYME DILUTION BUFFER

50mM Tris pH 7.5; 1mM DTT; 100mM NaCl; 10% glycerol; 1mg/ml BSA

ENZYME REACTION BUFFER

20mM Tris pH 7.4; 100mM NaCl; 1mg/ml BSA; 5mM $MgCl_2$; 2mM DTT

QUENCH BUFFER

125mM Tris pH 7.8; 75mM EDTA; 500mM KF; 0.125% Triton X-100; 1.25% BSA; 60 nM SA-XL665 (Packard); 300 pM europium cryptate labeled anti-phosphotyrosine antibody (Eu-PY20)

PEPTIDE SUBSTRATE

Sequence LCB-EQEDEPEGDYFEWLE-NH_2; stock solution is 1mM disolved in DMSO; diluted to 1uM in 1X enzyme reaction buffer for 10X working stock. (LCB = aminohexanoylbiotin)

ATP

Stock solution is 0.5 M ATP (Boehringer) pH 7.4; stock solution is diluted to 40mM ATP in enzyme reaction buffer to give 20X working stock solution

HEK-21 CELL LINE

Human embryonic kidney cells (HEK-293) (ATCC) were transfected with an expression plasmid containing the entire IGF-1R coding sequence. After antibiotic selection, colonies were screened for IGF-1R overexpression by western blot analysis. One clone, designated HEK-21 was selected for cell based IGF-1R autophosphorylation assays.

HEK CELL GROWTH MEDIA

Dulbecco's Modified Eagle's Media (DMEM), 10% Fetal Calf Serum, 1X Penn/ Strep, 1X Glutamine, 1X Non-essential amino acids (all from Life Technologies)

CELL LYSIS BUFFER

50mM Tris-HCl pH 7.4; 150mM NaCl; 1% Triton X-100 (Sigma); 1X Mammalian protease inhibitors (Sigma); 10mM NaF; 1mM NaVanadate

WESTERN BLOCKING BUFFER

20mM Tris-HCl pH 8.0; 150mM NaCl; 5% BSA (Sigma); 0.1% Tween 20 (Biorad)

METHODS

A. PROTEIN PURIFICATIONS

Spodoptera frugiperda SF9 cells were transfected with recombinant virus encoding either the GST-IGF-1R β-subunit or GST-InsR fusion protein at an MOI of 4 virus particles/cell. Cells are grown for 48 hours at 27°C, harvested by centrifugation and washed once with PBS. The cell pellet is frozen at –70°C after the final centrifugation. All subsequent purification steps are performed at 4°C. 10 grams of frozen cell paste is thawed in a 90ml volume of insect cell lysis buffer (BD-Pharmingen) and held on ice with occasional agitation for 20 minutes. The lysate is centrifuged at 12000g to remove cellular debris. Lysis supernatant was mixed with 45ml of glutathione agarose beads (BD-Pharmingen) and agitated slowly at 4°C for one hour after which the beads were centrifuged and washed 3X with wash buffer. The beads are resuspended in 45 ml of wash buffer and poured as a slurry into a chromatography column. The column is washed with 5 volumes of wash buffer and the GST-IGF-1R is eluted from the column with 5mM Glutathione in wash buffer. Pooled fractions are dialyzed vs. dialysis buffer and stored at -20°C.

B. IGF-1R KINASE ASSAY

The IGF-1R enzyme reaction is run in a 96 well plate format. The enzyme reaction consists of enzyme reaction buffer plus 0.1nM GST-IGF-1R, 100 nM peptide substrate and 2mM ATP in a final volume of 60 microliters. Inhibitor, in DMSO, is added in a volume 1 microliter and preincubated for 10 minutes at 22°C. Final inhibitor concentration can range from 100uM to 1nM. The kinase reaction is initiated with 3 microliters of 40mM ATP. After 20 minutes at 22°C, the reaction is stopped with 40 microliters of quench buffer and allowed to equilibrate for 2 hours at 22°C. Relative fluorescent units are read on a Discovery plate reader (Packard). IC50s for compounds are determined by 4 point sigmoidal curve fit.

C. INSULIN RECEPTOR KINASE ASSAY

The kinase reaction for insulin receptor is identical to that used to assay IGF-1R (above), except that GST-InsR is substituted at a final concentration of 0.1nM.

D. CELL BASED IGF-1R AUTOPHOSPHORYLATION ASSAY

IGF-1R inhibitor compounds are tested for their ability to block IGF-I induced IGF-1R autophosphorylation in a IGF-1R transfected human embryonic kidney cell line (HEK-21). HEK-21 cells over-expressing the human IGF-1R receptor are cultured in 6-well plates (37°C in a 5% CO_2 atmosphere) in HEK cell growth media to 80% of confluence. Cells are serum starved for four hours in HEK growth media with 0.5% fetal calf serum. A 10X concentration of inhibitor in growth media is added to the cells in one-tenth the final media volume and allowed to preincubate for one hour at 37°C. Inhibitor concentration can range from 10nM to 100uM. IGF-I (Sigma) is added to the serum starved cells to a final concentration of 30ng/ml. After a 10 minute incubation in the presence of IGF-I at 37°C, the media is removed, the cells washed once with PBS and 0.5mls of cold cell lysis buffer added. After 5 minutes incubation on ice, cells are scraped from the wells and lysis buffer plus cells are transferred to a 1.5ml microfuge tube. The total lysate is held at 4°C for twenty minutes and then centrifuged at top speed in a microfuge. The supernatant is removed and saved for analysis. Phosphorylation status of the receptor is assessed by Western blot. Lysates are electrophoresed on 8% denaturing Tris-Glycine polyacrylamide gels and the proteins transferred to nitrocellulose filters by electro-blotting. The blots are blocked with blocking reagent for 10 minutes after which anti-phosphotyrosine antibody (4G10, Upstate Biotechnology) is added to a final dilution of 1:1500. Blots and primary antibody are incubated at 4°C overnight. After washing with PBS plus 0.2% Tween 20 (Biorad), an HRP conjugated anti-mouse secondary antibody (Jackson Labs) is added at a dilution of 1:15000 and incubated at 4°C for 2 hours. Blots are then washed with PBS-Tween and developed using ECL (Amersham) luminescent reagent. Phosphorylated IGF-1R on the blots is visualized by autoradiography or imaging using a Kodak Image Station 440. IC50s are determined through densitometric scanning or quantitation using the Kodak Digital Science software.